

# ACTA MEDICA SCANDINAVICA

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## Sur un effet curieux de l'acide nicotique (hyperémie périarticulaire)

par

ERIK ASK-UPMARK, D<sup>r</sup> en médecine.

(Ce travail est parvenu à la rédaction le 23 Décembre 1942).

Dans un travail précédent, l'auteur a signalé à l'attention le singulier effet vaso-moteur, avec sensation de chaleur, qui accompagne souvent l'administration de l'acide nicotique. Cet effet est particulièrement prononcé au cou, aux bras et aussi, à un moindre degré, aux jambes. L'effet produit sur les bras est surtout remarquable et a pu être utilisé, comme l'auteur l'a montré, pour le traitement de certains troubles vaso-moteurs, notamment de l'acrocyanose. Il consiste en une sensation de forte chaleur, accompagnée de rougeur de la peau, et diversement accusée dans les différents cas, mais qui est particulièrement forte en général lorsque l'acide nicotique a été administré à jeun, c'est-à-dire entre les repas. La dose employée était de 50 à 100 mg d'acide nicotique 3 fois par jour.<sup>1</sup> La rougeur visible était le plus prononcée, dans la règle, aux parties latérales du cou, aux épaules et vers le bas de bras; elle était moins apparente aux doigts, mais c'est là, par contre, que la sensation de chaleur était la plus forte. L'auteur constatait aussi que l'acide nicotique peut être administré avec avantage aux malades atteints d'affections articulaires dont le processus est objectivement localisé pour l'essentiel dans les parties molles des tissus périarticulaire, et se manifeste subjectivement avant tout par de la rigidité et

<sup>1</sup> Les préparations employées étaient le «nipellan» (de la fabrique Pharmacia à Stockholm) et l'acide nicotique «Ido» (de la fabrique Ferrosan à Malmö).

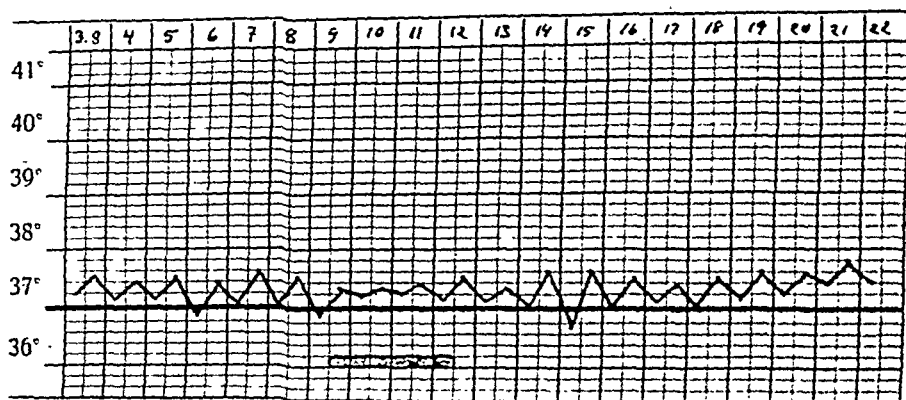
de la raideur dans les doigts le matin: l'acide nicotique rendait en pareils cas le même service qu'un bain de mains chaud et assouplissait les articulations, que l'on pouvait soumettre alors à des exercices.

Le présent travail a pour but de rendre compte d'un cas où, grâce à diverses circonstances, l'effet susvisé de l'acide nicotique a pu être tout particulièrement bien observé. «Beware of the man who has one case to report», disait avec raison le vieux Mayo. Il n'en est pas moins vrai que précisément l'étude approfondie d'un cas spécial est parfois plus instructive que la réunion d'une documentation nombreuse. L'histoire de la médecine offre bien des exemples du fait: il suffira de rappeler ici le cas d'hyperparathyroïdisme opéré pour la première fois par Mandl.

Mlle I. A., 31 ans, observée aux bains de Ramlösa (Suède) en juillet—août 1942. Antérieurement bien portante. A été atteinte il y a 4 ans d'une maladie, qui provoqua une forte élévation de la température et que l'on crut alors être une pneumonie. Fut soignée pour cette affection dans un hôpital pendant 6 semaines, mais sans que la température redescendît à son niveau normal. Maigrit à cette occasion de 15 kg, diminution de poids qui a persisté depuis lors. Présenta à plusieurs reprises au début de la maladie de la diplopie, mais qui ne reparut pas ensuite. Sommeil tantôt bon, tantôt mauvais. A beaucoup souffert de migraines ces dernières années. Avait souvent, au début de l'affection, des douleurs, dans l'épigastre et des vomissements. Menstruation faible mais fréquente (20 jours d'intervalle). Souffrait déjà au début de la maladie de douleurs très prononcées dans les bras et les jambes, lesquelles persistèrent, mais à un moindre degré: elle pouvait à peine marcher à son retour de l'hôpital, tant la hanche lui faisait mal. En janvier 1941, tous les doigts enflèrent, bleuïrent et prirent un aspect brillant; on crut à la possibilité de l'existence du mal de Poncet, car le père avait eu la tuberculose; mais la radioscopie des poumons ne fit apparaître qu'un petit foyer complètement stationnaire dans la région de la clavicule droite, foyer qui depuis lors est inchangé. L'épreuve sur le cobaye a donné un résultat négatif. Les doigts se sont améliorés depuis lors, mais leurs articulations restent un peu enflées. La malade a éprouvé ces dernières années une sensation de grande fatigue. La réaction de sédimentation a oscillé en ces dernières années entre 6 et 10 par heure. Ni soif ni polyurie en aucun cas.

*Etat:* Jeune femme très maigre, taille 167 cm, poids 44 kg. L'aspect huileux pommadé (Salbengesicht, greasy face), mais pas de masque facial. Température subfébrile (voir les courbes de fièvre ci-dessous, qui montrent que l'élévation de température n'est pas seulement prémenstruelle). Tachycardie 100 environ, aucune autre altération physique du cœur ou des poumons; la radioscopie du thorax révèle un état normal. La malade est

passablement nerveuse, réaction de sédimentation 9, tension artérielle 150/100. Signe de Hoffmann à la main droite positif, réflexes patellaires fortement accrus, signe de Babinski négatif, ophtalmoscopie sans rien d'anormal. Rétropulsion. Morphologie sanguine: hémoglobine 71, globules rouges 3.74 millions, leucocyte 6400. Métabolisme basal + 22 %. Articulations: les articulations interphalangiennes des doigts présentent un léger épaissement péri capsulaire, mais sans coloration anormale ni réduction de la mobilité; rien d'autre à signaler du côté des articulations. La thyroïde ne donne lieu à aucune observation.



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Courbe de la température pour la période 3—22. 8. Du 9 au 12. 8. menstruation. La température subfebrile indépendante de la menstruation.

Dans le cas ici considéré, le diagnostic encéphalite ou état post-encéphalitique paraît certainement le plus plausible. L'élévation de température persistante, la diplopie au début de l'affection, les migraines, les douleurs dans différentes parties de l'organisme, l'amaigrissement prononcé, le facies luisant, les constatations neurologiques positives, autant de symptômes qui semblent le mieux concorder avec ce diagnostic. En ce qui concerne les doigts, on peut se demander si l'encéphalite constituait peut-être une manifestation d'une affection rhumatismale (affections qui, telles que la chorée, attaquent souvent le cerveau), ou si les altérations articulaires sont un phénomène secondaire de l'encéphalite, dans le sens où l'entendent certains auteurs (Lichtwitz, etc.). Quoi qu'il en soit, il fut décidé de soumettre provisoirement la malade à un traitement des symptômes: du fer pour combattre l'anémie, de la diiodthyrosine  $0.1 \times 3$  contre l'hyperthyroïdisme, dont on ne croyait pas pouvoir exclure totalement l'existence, et du «nipellan» (ou acide nicotique) à employer principalement pour essayer d'obtenir une hyperémiasation des mains froides (et ne rappelant nullement la maladie de

Basedow). Or, il se produisit ce fait remarquable que toutes les fois qu'elle prit du «nipellan» (50 à 100 g d'acide nicotique 3 fois par jour), la malade éprouva une sensation générale de chaleur et une hyperémie active très marquée, laquelle était exclusivement localisée dans la peau des articulations des extrémités, tandis que la région interarticulaire en était totalement exempte: on ne constata par ailleurs qu'une certaine rougeur des parties latérales du cou, du lobe des oreilles et, fortement accusée, de la peau du manubrium sterni. L'effet produit était très curieux à observer: 10 minutes après l'absorption de l'acide nicotique, la malade éprouvait une certaine sensation de froid et pâlisait, et 7 minutes plus tard apparaissait la rougeur mentionnée ci-dessus, tout d'abord au cou, puis sur les côtés postérieur et surtout antérieur du coude (mais non sur les parties latérales), ensuite aux articulations des épaules, des poignets et des genoux, plus tard encore à l'articulation métacarpo-phalangienne du pouce et aux articulations talocrurales (aux deux malléoles), et pour finir aux autres articulations des doigts. En même temps la tension artérielle diminuait quelque peu (passant de 140/90 à 120/80) et une agréable sensation de chaleur envahit l'organisme. On avait l'impression d'avoir devant soi une femme aux articulations tatouées en rouge.

Il est difficile de se prononcer sur le rôle joué par l'encéphalite présumée dans l'apparition du phénomène ici considéré. D'une part, l'hyperémie cutanée est particulièrement accusée aux épaules et aux bras, ce qui se constate habituellement en cas d'absorption d'acide nicotique (Ask-Upmark). D'autre part, l'électivité marquée à la peau des régions articulaires n'est guère apparue de la même façon dans les cas observés auparavant. On a déjà rappelé qu'un groupe de savants ont voulu placer dans le tronc cérébral le substratum primaire de l'infection rhumatismale et spécialement de la maladie de Still. Lors même que différentes raisons, telles que la présence de nodules d'Aschoff dans le myocarde et les capsules articulaires rendent le fait peu probable, il faut bien présumer qu'il existe une connexion étroite entre le tronc cérébral et notamment de sa partie diencéphale, d'une part, et, de l'autre, les articulations: elle est attestée, d'un côté, par l'apparition de la chorée à la suite de l'infection rhumatismale, cependant que, d'un autre côté, l'on a lieu de tenir a priori pour probable l'existence d'un lien entre le centre de règlement de la température et de la leucopoièse et les organes mésenchymaux d'exécution de la réaction allergique (cf. la fièvre

et l'affection polyarticulaire de la maladie de sérum). On peut concevoir, il est vrai, que cette coïncidence ne serait qu'apparente, et que ce qu'il y a de commun dans les phénomènes en question doit être cherché dans un engagement des vaisseaux, si caractéristique, on le sait, dans l'infection rhumatismale. Quoi qu'il en soit, le fait mérite d'être retenu que certains estiment que l'acide nicotique ou son amide exerce son effet par le tronc cérébral, et, en outre, que les altérations cutanées du manubrium (où la rougeur était particulièrement marguée) peuvent être très caractéristiques dans l'encéphalite. Il semble bien, à la lumière de ces faits, que l'observation ici considérée puisse constituer une contribution, assez modeste, il est vrai, à l'étude de la biologie des structures périarticulaires. Il appartiendra aux recherches ultérieures de dire si notre observation peut être utilisée en thérapeutique: les expériences que nous avons déjà faites à cet égard (voir ce qui précède) paraissent encourageantes.

### Résumé.

L'auteur décrit le cas d'une femme de 31 ans, souffrant depuis 4 ans d'un état post-encéphalitique et qui réagit à l'administration d'acide nicotique par une intense hyperémie cutanée, exclusivement localisée dans la peau des articulations des extrémités. Il effleure, dans la discussion du cas, la question d'un lien éventuel entre le tronc cérébral et les articulations.

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## Frequenz und Dauer der subjektiven Wirkungen und Nebenwirkungen von Benzedrin und Pervitin bei hochgradiger Ermüdung.

Von

NILS ALWALL.

(Bei der Redaktion am 26 Oktober 1942 eingegangen.)

Über die Wirkungen, die Benzedrin ( $\beta$ -Phenylisopropylamin) und Pervitin (N-Methyl- $\beta$ -phenylisopropylamin) auf nicht ermüdete Personen haben, liegt ein reiches Schrifttum vor, und zwar sowohl was den subjektiven Effekt dieser Pharmaka als ihre Wirkungen auf psychische Funktionen betrifft (Bourdon-Tests, Rechenproben usw.). Auch der Einfluss auf die physische Leistungsfähigkeit ist untersucht worden, hauptsächlich jedoch an vorher nicht oder verhältnissmässig wenig ermüdeten Menschen.

In einer folgenden Arbeit (Alwall, 1943) werden Studien an einem grösseren Material über die Einwirkung von Benzedrin und Pervitin auf die physische und die psychische Leistungsfähigkeit hochgradig ermüdeter Menschen vorgelegt.

Hier werden Untersuchungen über die subjektiven Wirkungen und Nebenwirkungen von Benzedrin und Pervitin an demselben Material mitgeteilt. Die Resultate dieser an hochgradig ermüdeten Menschen ausgeführten Untersuchungen veranlassen eine Überprüfung gewisser Angaben über die Wirkungen und Nebenwirkungen dieser Mittel, von denen einige als so sicher betrachtet worden sind, dass man sie schon in den Lehrbüchern findet. Auch ein Vergleich zwischen den Wirkungen von Benzedrin und Pervitin unter

Besonderer Berücksichtigung der Wirkungsstärke und der Nebenwirkungen ist im Rahmen dieser Untersuchung ausgeführt worden. Ein solcher Vergleich liegt bisher im einschlägigen Schrifttum nicht vor.

Die Darstellung der Versuchsergebnisse gliedert sich folgendermaßen:

Material, Ermüdung.

Kap. I. Studien über die subjektiven Wirkungen und Nebenwirkungen des Benzodrin und Pervitins bei hochgradiger Ermüdung.

Kap. II. Vergleich zwischen Benzodrin und Pervitin mit Rücksicht auf die Wirkungen und Nebenwirkungen.

### Material, Ermüdung.

720 wohltrainierte Soldaten, hauptsächlich im Alter von 20—22 Jahren wurden durch Daueranstrengungen während dreier Nächte und an den Zwischentagen fast ohne Schlaf hochgradig ermüdet. Eine folgende Arbeit, Alwall, 1943, gibt die wesentlichen Einzelheiten der Ermüdungsübungen.

Die Teilnehmer waren auf 6 Übungskompanien verteilt. Die Teilnehmernummern von 1 bis 720 wurden so verteilt, dass jede Kompanie gleichmäßig viele Nummern aus den verschiedenen Versuchsserien zugewiesen bekam (Tabelle 1). Der erste Mann der Kompanie erhielt eine Nummer aus

Tabelle 1.

Verteilung der Teilnehmernummern und Tabletten.

B = Benzodrin, P = Pervitin, 3. Tag = Morgen des vorletzten Tages, 4. Tag = Morgen des letzten Tages.

Versuchs- serie	1.	2.	3.	4.	5.	6.
<i>Tabletten:</i>						
3. Tag	—	—	—	—	20 mg B	20 mg B
4. Tag	Leertabl.	20 mg B	30 mg B	18 mg P	20 mg B	Leertabl.
<i>Teilnehmer- nummern:</i>						
1. Komp.	1—20	121—140	241—260	361—380	481—500	601—620
2. Komp.	21—40	141—160	261—280	381—400	501—520	621—640
3. Komp.	41—60	161—180	281—300	401—420	521—540	641—660
4. Komp.	61—80	181—200	301—320	421—440	541—560	661—680
5. Komp.	81—100	201—220	321—340	441—460	561—580	681—700
6. Komp.	101—120	221—240	341—360	461—480	581—600	701—720

der niedrigsten Serie, der zweite Mann eine Nummer aus der nächsthöheren Serie usw. Hierdurch bekam man die Gewähr, dass die Versuchspersonen aller Tablettenserien gleichmässig stark angestrengt wurden. Das Übungsprogramm aller Kompanien war dasselbe und die Anstrengungen somit nach Möglichkeit die gleichen; etwaige Unterschiede wurden durch die Verteilung der Personennummern in der angegebenen Weise ausgeglichen.

Die einzelnen Serien bekamen ihre Tablettenzuteilung gemäss Tab. 1. Die Versuchspersonen der Serien 1—4 erhielten die Tabletten erst am Morgen des letzten Tages um 6 Uhr, die der Serien 5 und 6 bekamen 20 mg Benzodrin am Morgen des vorletzten Übungstages um 8 Uhr; Serie 5 bekam ausserdem die gleiche Dosis am Morgen des letzten Tages, Serie 6 statt dessen Leertabletten. Sämtliche Versuchsteilnehmer bekamen die Tabletten nach einer leichteren Mahlzeit. Die Serien 3 und 4 erhielten erst jedoch nur zwei Drittel ihrer Dosis und den Rest etwa  $\frac{1}{2}$  Stunde später, um Nebenwirkungen bei zu schneller Resorption einer grossen Dosis zu vermeiden.

Um die Wirkung von Benzodrin und Pervitin zu vergleichen, bekamen die Serien 2—4 20 oder 30 mg Benzodrin bzw. 18 mg Pervitin. Zwar liegen Angaben vor, Pervitin sei doppelt so wirksam wie Benzodrin, Vorversuche liessen aber als wahrscheinlich erkennen, dass die Wirkungskraft etwa dieselbe ist. Deshalb wurde die genannte Dosis gewählt, da nur eine Versuchsserie für Pervitin, dessen Tabletten je 3 mg enthielten, zur Verfügung stand. Dadurch boten sich folgende Vergleichsmöglichkeiten: ist die Wirkung von 18 mg Pervitin gleich der Wirkung von 20 mg Benzodrin oder grösser, bzw. erreicht sie die Wirkung von 30 mg Benzodrin?

Diejenigen, die sich während der Übungen krank meldeten, wurden sofort ärztlich untersucht. Der Gesundheitszustand während der Übungen war gut, A. 1943. Es wurde besonders nachgeprüft, dass die Vp. auch die angegebenen Tabletten bekamen. Einige Fälle, bei denen die Ergebnisse aus diesem oder jenem Grunde unzuverlässig erschienen, wurden von der Bearbeitung ausgenommen. Die Vp. bekamen natürlich nicht zu wissen, dass es verschiedene Tabletten gab. Es wurden ihnen mitgeteilt, dass es sich um »Nährtabletten« handelte.

## Kap. I.

### Studien über die subjektiven günstigen Wirkungen und ungünstigen Nebenwirkungen des Benzodrins und Pervitins bei hochgradiger Ermüdung.

Den Versuchspersonen wurden Fragen (Fragebogen) über die subjektiven Wirkungen des Benzodrins (und Pervitins) am vorletzten und letzten Tage vorgelegt, die mit Ja oder Nein zu beantworten waren.



worten waren, von den Fragen nach der Dauer der Wirkungen abgesehen. Die Fragen wurden in erforderlichem Umfang kommentiert.

### 1. Günstige Wirkungen.

#### A. Die Wirkung des am Morgen des letzten Tages eingenommenen Benzadrins und Pervitins am selben Tage.

Der Grad der Ermüdung nach Beendigung der Ermüdungsübungen und vor der Tablettenzuteilung ist aus Tabelle 2 zu sehen. In sämtlichen Serien sind die Zahlen etwa dieselben.

Tabelle 2.

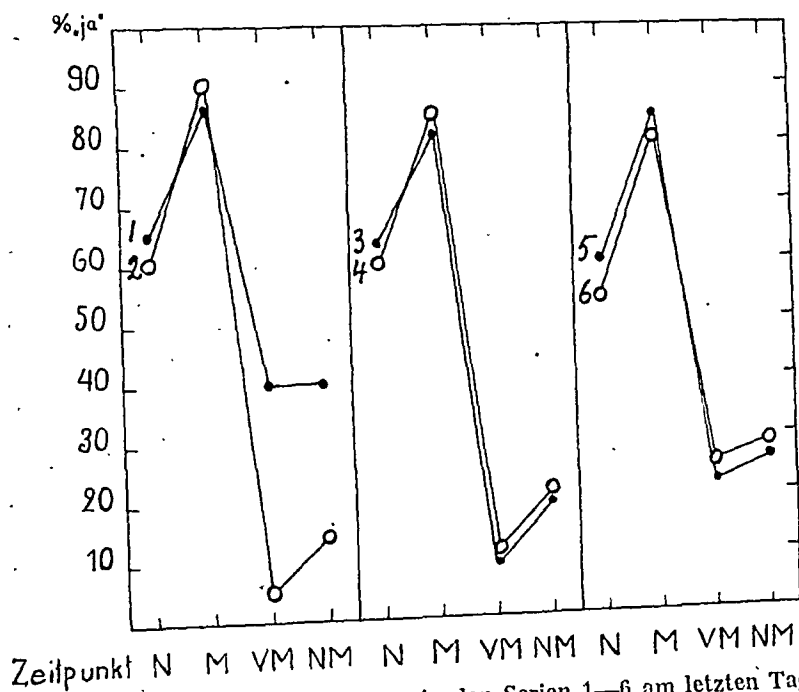
Das subjektive Befinden am Morgen des letzten Versuchstages vor dem Einnehmen der Tabletten.

Versuchsserie	1.	2.	3.	4.	5.	6.
Anzahl der Vp., von denen Antworten vorliegen .....	105	108	113	100	92	110
Von diesen Versuchspersonen meldeten (in Prozent):						
Müdigkeit .....	88	92	85	83	86	86
Schläfrigkeit .....	94	94	85	84	83	81
Unlust .....	63	69	70	57	64	65
Verminderte Merkfähigkeit ..	59	66	70	54	64	54
Schwierigkeit, den letzten Teil der Übungen wegen grosser Müdigkeit durchzuführen .....	50	42	50	42	42	38

Die Ergebnisse der Serien 5 und 6 werden erst unter B besprochen. Die Serien 2—4 werden erst in Kap. II untereinander verglichen; hier werden sie unter der gemeinsamen Bezeichnung Benzadrin-Pervitin-Serien zusammengefasst.

Figur 1 veranschaulicht die Häufigkeit lästiger Müdigkeit am letzten Tage vor und nach dem Einnehmen der Tabletten. In der Kontrollserie litten während des letzten Nachtmarsches 65 % unter schwerer Müdigkeit, vor der Tablettenausgabe 88 %, am Vormittag desselben Tages 41 %, und dieser Wert bleibt bis zum Nach-

mittag konstant. Die entsprechenden Prozentsätze in den Benzdrin-Pervitin-Serien sind: etwa 60 % beim Nachtmarsch, 83—92 % morgens vor der Tablettenausgabe. Am Vormittag nur 5—8 %, am Nachmittag etwas mehr, 14—23 %. Somit tritt ein spontaner Rückgang der Müdigkeit im Laufe des Tages ein, der jedoch in keiner Weise der Abnahme entspricht, die nach Benzdrin und Per-



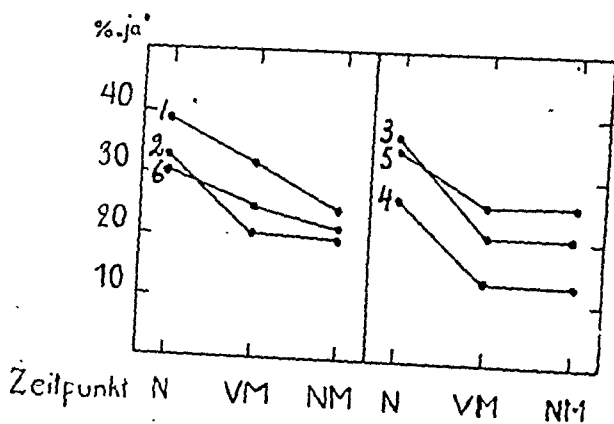
Figur 1. Angaben über Müdigkeit in den Serien 1—6 am letzten Tage. Die x-Achse gibt den Zeitpunkt an: Nacht, Morgen (vor dem Einnehmen der Tabletten), Vormittag und Nachmittag. Die y-Achse gibt die Anzahl der Vp. in Prozent an.

vitin verzeichnet werden kann. Die Wirkung dauert auch am Nachmittag, also noch nach etwa 10 Stunden an.

Figur 2 zeigt die Schwankungen in der Häufigkeit des Symptoms *Muskelschmerzen*. In der Kontrollserie geben nachts 39 % dieses Symptom an, am Vormittag 32 % und am Nachmittag 24 %. In den Benzdrin-Pervitin-Serien sind die entsprechenden Zahlen 26—38 %, 12—20 % und 12—21 %; also eine etwas kleinere Frequenz des Symptoms am Vormittag, der sich am Nachmittag im ganzen ausgeglichen hat (im Vergleich zur Kontrollserie).

Die Einwirkung der Tabletten auf ein anderes schmerzbetontes Erlebnis, die *Fussbeschwerden*: am Morgen des letzten Tages,

vor dem Einnehmen der Tabletten, wurde eine Besichtigung der Füße vorgenommen. Es meldeten sich in den verschiedenen Serien etwa 10 (9.2—11.8) % der Versuchspersonen. Die %-Zahl derjenigen, die wegen Fussbeschwerden von der Teilnahme am Geländelauf befreit wurden, beträgt in den Benzodrin-Pervitin-Serien: Ser. 2: 7.3, Ser. 3: 5.8 und Ser. 4: 7.0; in der Kontrollserie: 4.5 %. Die betreffenden Versuchspersonen hatten Blasen an den Füßen oder andere Schäden, die beim Laufen eine wesentliche Behinderung bedeuten mussten. Diese Zusammenstellung ist auch für das Ergebnis des Geländelaufs (Alwall, 1943) von Interesse. Sie zeigt nämlich

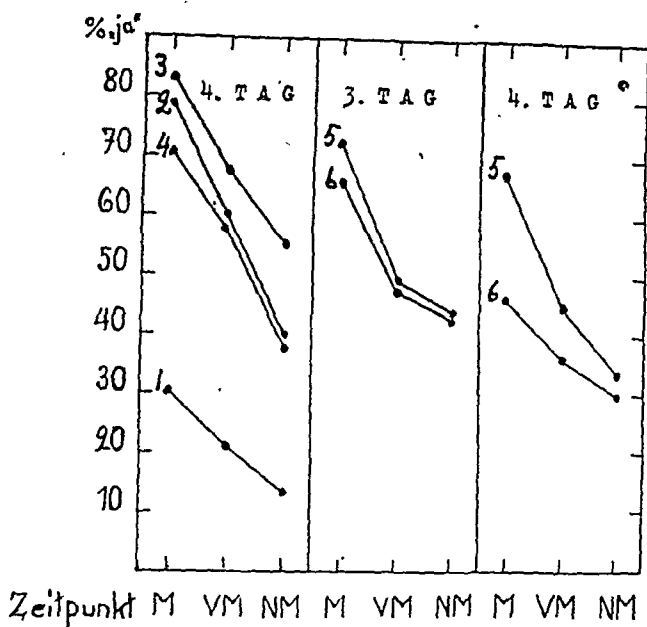


Figur 2. Muskelschmerzen am letzten Tage. Die x-Achse gibt den Zeitpunkt an: Nacht (also vor dem Einnehmen der Tabletten), Vormittag und Nachmittag.

teils, dass Fusschäden in sämtlichen Serien in etwa demselben Ausmass vorkamen, und teils, dass das in den Benzodrin-Pervitin-Serien festgestellte bessere Ergebnis nicht auf einer strengeren Auscheidung von Versuchspersonen mit Fusschäden beruht. In diesem Zusammenhang sind die Angaben über die Versuchspersonen von Interesse, die der Meinung waren, die Fusschäden hätten ihre Zeit beim Geländelauf verschlechtert. 33 % der Kontrollserie entsprechen etwa halb so viele in den Benzodrin-Pervitin-Serien: Ser. 2 18 %, Ser. 3 19 und Ser. 4 16 %. Das heisst, dass die heitere und euphorische Stimmung die Fusschäden weniger schmerzhaft erleben und damit auch ein geringeres Hindernis beim Geländelauf sein lässt. Dies ist für den Vergleich mit den Häufigkeitszahlen der Muskelschmerzen von Interesse.

Aus Figur 3 ersieht man Häufigkeit und Dauer euphorischer

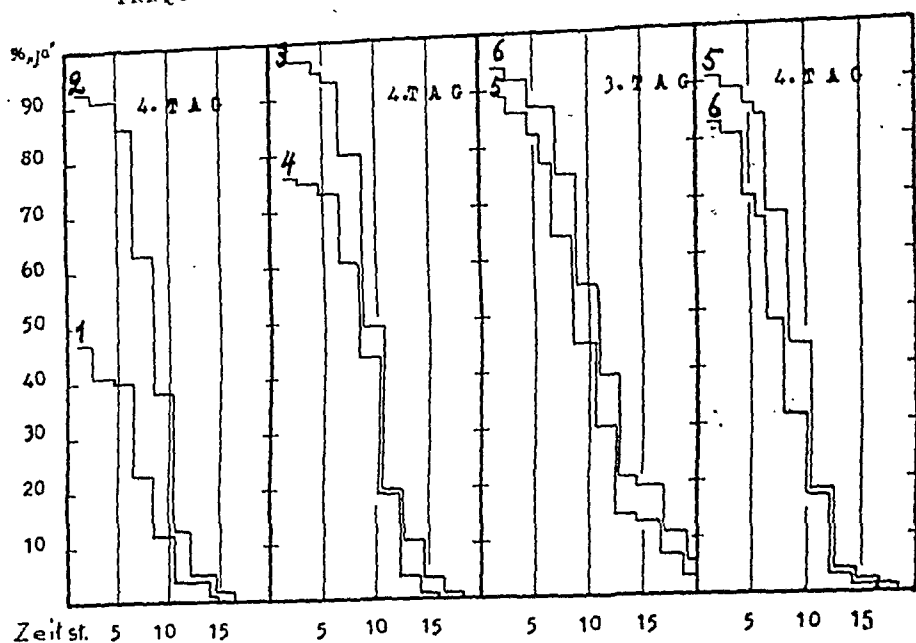
*Stimmungen* nach dem Einnehmen der Tabletten. Es versteht sich von selbst, dass auch Versuchspersonen der Kontrollserie nach vollbrachter Durchführung des anstrengenden Übungsprogramms fröhlich waren und erhöhtes Selbstvertrauen und Zuversicht an den Tag legten. In der Kontrollserie zeigten sich diese Stimmungen: morgens bei 31 %, im Laufe des Tages bei 21–14 %. Entsprechend in den Benzedrin-Pervitin-Serien: 70–79 %, 58–68 % und



Figur 3. Angaben über gehobene Stimmung (Heiterkeit, erhöhtes Selbstvertrauen, Zuversicht) in den Serien 1–6 am letzten Morgen, 2 Std. nach dem Einnehmen der Tabletten, sowie am Vormittag und Nachmittag. Die x-Achse gibt den Zeitpunkt an, die y-Achse die Anzahl der Vp. in Prozent.

38–55 %. Wir finden hier also eine ausgeprägte Hebung der Stimmung, die zwar im Laufe des Tages ein wenig nachlässt, aber noch gegen Abend unverkennbar andauert.

Figur 4 veranschaulicht die Dauer *günstiger Wirkungen irgendwelcher Art* während des letzten Tages durch die am Morgen eingenommenen Tabletten. Diese Frage wurde mit Rücksicht darauf gestellt, dass es den ungeschulten Teilnehmern schwerfällt, sichere Antworten auf mehr ins einzelne gehende Fragen abzugeben. Der unmittelbare suggestive Effekt der Leertabletten in Serie 1 nimmt anfangs ein wenig ab, bleibt dann 5–6 Stunden konstant und nimmt dann wieder sukzessiv stark ab. Diese Kurve zeigt die nor-



Figur 4. Häufigkeit und Dauer der günstigen Tablettenwirkungen am vorletzten (3.) und letzten (4.) Tage nach dem Einnehmen der Tabletten an den betreffenden Tagen. Die x-Achse gibt die Wirkungsdauer in Stunden an, die y-Achse die Anzahl der Vp. in Prozent. Die eingezeichneten Zahlen geben die Serien an, auf die sich die Kurven beziehen.

male Variation der Müdigkeit im Laufe des Tages (Kleitman, 1939; siehe Alwall, 1943) was die Vp. ganz selbstverständlich mit den Tabletten in Verbindung bringen.

In den Benzodrin-Pervitin-Serien liegen die Zahlen schon von Anfang an auf grösserer Höhe und fallen langsamer ab als in der Kontrollserie. In der Kontrollserie dauert der günstige Effekt durchschnittlich 3.3 Stunden an, in den Benzodrin-Pervitin-Serien 6.4—8.4 Stunden; das Übergewicht der letzteren ist gesichert.

In diesen Versuchen ist also bei einer nicht geringen Anzahl von Vp. eine *mindestens 12 Stunden anhaltende Wirkung der Tabletten* festgestellt worden. Indessen gewinnt man dadurch kein zuverlässiges Bild davon, wie lange die Benzodrin- bzw. Pervitinwirkung andauern kann, denn die Observationszeit wird durch das Zubettgehen der Vp. am Abend des letzten Versuchstages begrenzt.

*B. Die Wirkung des am Morgen des vorletzten Tages verabfolgten Benzedrins an demselben und dem folgenden Tage.*

Die folgende Diskussion geht aus von einem Vergleich zwischen Serie 1 und den Serien 5 und 6 am vorletzten und letzten Tage des Dreinächteversuchs. Die Vp. der letzteren beiden Serien bekamen am Morgen des vorletzten Tages 20 mg Benzedrin und am Morgen des letzten Tages nochmals 20 mg Benzedrin (Ser. 5) bzw. Leertabletten (Ser. 6).

Figur 4 veranschaulicht auch die Häufigkeit und Dauer *günstiger Wirkungen irgendwelcher Art am dritten Tage* nach der Einverleibung von Benzedrin am Morgen desselben Tages in Serie 5 und 6. Trotz der zu diesem Zeitpunkt der Übungen noch weniger starken Ermüdung hat die Dosis von 20 mg Benzedrin am dritten Tage etwa dieselbe Wirkung wie die erst am letzten Tage den Vp. der Serie 2 verabfolgte gleich grosse Dosis. Die günstige Wirkung besteht am dritten Tage mindestens 4 Stunden lang in 82—86 % der Serien 5 und 6 (90 % am vierten Tage in Serie 2), mindestens 8 Stunden in 64—67 % (63 %) und mindestens 12 Stunden in 30—18 % (11 %). Die Wirkung scheint also am letzten Tage etwas schneller abgeklungen zu sein, was auch in dem Mittelwert der Wirkungsdauer, 7.8—8.5 Stunden (6.4), zum Ausdruck kommt. Hier muss jedoch die kürzere Observationsdauer in Serie 2 berücksichtigt werden, da die Versuchspersonen dieser Serie abends zu Bett gingen, während die Übungen in der auf den dritten Tag folgenden Nacht weitergingen, weshalb die Prozentzahlen nach 12 Stunden am vierten Tag und die Mittelwerte der Wirkungsdauer unzuverlässig sind.

*Die Frage nach der Dauer der Benzedrinwirkung* muss durch Serie 6 beantwortet werden. Serie 6 wollen wir mit Serie 1 vergleichen. Beide bekamen am letzten Tage Leertabletten, doch hatte Serie 6 am Vortage 20 mg Benzedrin bekommen. Lässt sich eine fortdauernde Wirkung dessen erkennen?

Wir sehen in Figur 4 bei Serie 6 am vierten Tag eine Wirkung der Leertabletten, die annähernd der in Serie 2 beobachteten entspricht und erheblich über der in Serie 1 liegt. Die Wirkung dauert 6.3 Stunden an (in Serie 1 3.3 Stunden); günstige Wirkung während

mindestens 4 Stunden melden 70 (41) %, während 8 Stunden 48 (23) %, während 12 Stunden 17 (3) %. Entschiedenem Nutzen der Tabletten wollen 68 (40) % verspürt haben. Es liegt also eine seit dem Vortage andauernde Benzodrinwirkung in Serie 6 vor, die einen langdauernden suggestiven Effekt der Leertabletten gestattet.

Figur 1: Die Müdigkeit ist bei den Vp. der Serie 6 während der letzten Nacht vielleicht etwas geringer als in Serie 1: 54 (65) %. Während am Morgen die Müdigkeit praktisch die gleiche ist, liegen die Werte der Serie 6 sowohl am Vormittag als am Nachmittag des letzten Tages erheblich unter denen der Serie 1: 24 (41) bzw. 27 (41) %. Dies besagt, dass die Vp. der Serie 6 sich in einer besseren Ausgangslage befinden und sich im Laufe des Tages besser erholen. — Die prozentuale Häufigkeit der Muskelschmerzen ist in Serie 6 etwas niedriger, wenigstens am Vormittag.

Figur 3: Am dritten Versuchstage zeigen die Serien 5 und 6 Euphorie (Heiterkeit, Selbstvertrauen, Zuversicht) im selben Ausmass wie Serie 2 nach der Dosis des letzten Tages. Trotz der ungleich hochgradigen Ermüdung ist die Reaktion also gleich stark. Die Zahlen der Serie 6 liegen am letzten Tage durchweg bedeutend über denen der Serie 1.

*Trotz der im Laufe des Versuchs zunehmenden Müdigkeit, die in Serie 6 sicherlich grösser ist als in Serie 1 (siehe unten!), üben 20 mg Benzodrin, die am Morgen des dritten Versuchstages verabfolgt wurden, noch etwa 36 Stunden später eine deutliche Wirkung.*

Wäre diese Dosis bei geringerer Ermüdung verabfolgt worden so dürfte man mit einer noch längeren Wirkungsdauer haben rechnen können.

Die Frage nach der Wirkung wiederholter Benzodrindosen kann durch Serie 5 studiert werden, die am vorletzten und letzten Tage 20 mg Benzodrin bekam. Diese Serie wird mit Serie 2 verglichen, die nur am letzten Tage 20 mg Benzodrin bekommen hat.

Die günstige Wirkung irgendwelcher Art (Fig. 4) dauert in Serie 5 durchschnittlich 9.4 Stunden an (6.4 Std in Serie 2), und 38 (11) % haben mindestens 12 Stunden lang eine günstige Wirkung verspürt. Die Wirkung der wiederholten Dosis ist also etwas grösser.

Tabelle 3.

Die günstigen Wirkungen von 20 mg Benzdrin (Ser. 2), 30 mg Benzdrin (Ser. 3) und 18 mg Pervitin (Ser. 4) im Dreinächteversuch. Die Angaben sind den weiter oben veröffentlichten Resultaten entnommen. Für Ser. 2 werden die absoluten Werte aufgeführt, für die übrigen Serien die Abweichungen von diesen Werten. Für die subjektiv günstigen Wirkungen sind die Werte in % angegeben, für den Geländelauf in Sekunden. Bezüglich Muskelschmerzen und Lauf gehen positive Zahlen Verminderung der Werte = bessere Ergebnisse an. Die Tabelle will eine Übersicht über die Unterschiede geben.

	Serie 2. 20 mg Benzdrin	Unterschied gegenüber Serie 2	
		Serie 3. 30 mg Benzdrin	Serie 4. 18 mg Pervitin
Ausgeruht vorm. ....	22	+12	+ 5
Muskelschmerzen vorm. ....	20	+ 8	—
gehobene Stimmung vorm. ....	78	+ 5	— 7
nachm. ....	71	+ 7	— 3
abends ....	50	+16	— 2
günstige Wirkung 2 Stdn. ....	93	+ 5	—17
4   "   ....	90	+ 5	—17
8   "   ....	63	+17	— 2
12  "   ....	11	+ 9	+ 7
entschiedener Nutzen der Tabl. ..	87	+ 6	— 4
Geländelauf (Alwall, 1943)	10	+44	+14

Müdigkeit und Muskelschmerzen (Fig. 1 und 2): die günstige Wirkung in Serie 5 ist etwas geringer als in Serie 2. Dasselbe gilt von der euphorischen Stimmung, Fig. 3.

Die hier angeführten Ergebnisse stellen zwar nicht mit Sicherheit eine Kumulation der Wirkung bei der nach 24 Stunden wiederholten Benzdrinverabfolgung fest, andererseits aber erlauben die Versuchsbedingungen nicht den Schluss, dass die zweite Dosis weniger wirksam sei als die erste.

Unter dem Einfluss der ersten Benzdrindosis dürften die Vp. Serie 5 (ebenso Serie 6) am dritten Tage und in der folgenden Nacht eine stärkere Aktivität entwickelt und die kurzen Pausen für Ruhe und Entspannung weniger ausgenutzt haben als die übrigen. Deshalb dürften die Kräfte-reserven bei diesen Serien am vierten Tage kleiner gewesen sein, wenn dies auch vielleicht durch die seit dem Vortage andauernde Benzdrinwirkung verdeckt wird. Man



dürfte daher unter diesen Bedingungen von vornherein mit folgenden Möglichkeiten zu rechnen haben: 1) dass dieselbe Dosis bei den stärker ermüdeten Vp. trotz etwaiger Kumulation eine geringere Wirkung auslöst, so dass in Serie 5 eine grössere zweite Dosis erforderlich wäre, um dieselbe Wirkung zu haben als die, die sich bei 20 mg Benzodrin am letzten Tage in Serie 2 ergab; 2) dass die in Serie 5 ermüdeten Vp. überhaupt nicht mehr in gleichem Masse auf Benzodrin zu reagieren vermögen wie Serie 2.

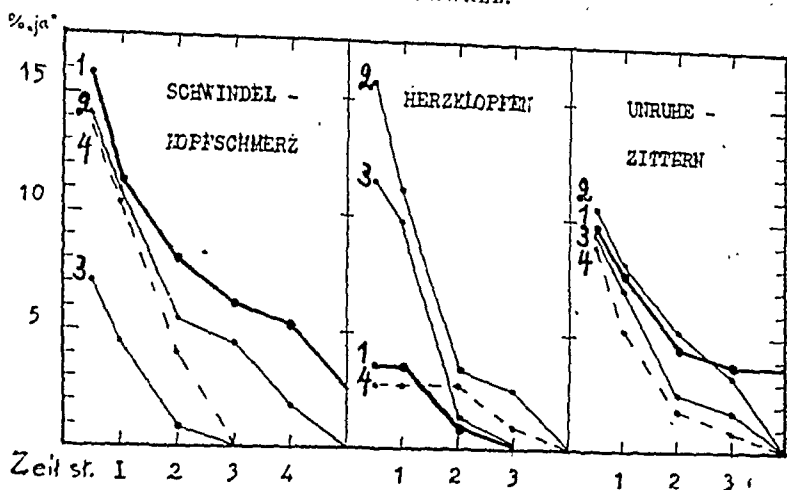
3) Die Möglichkeit, dass die vom Vortage noch andauernde Benzodrinwirkung zusammen mit der am letzten Tage verabfolgten Dosis Überdosierung verursacht hat, muss mit in Betracht gezogen werden. Dabei könnten — wie weiter unten ausgeführt wird — die bei der Überdosierung auftretenden Nebenwirkungen die günstigen Wirkungen überdecken, so dass letztere anscheinend in geringerer Frequenz auftreten. Figur 5 zeigt, dass Kopfschmerz und Schwindel am letzten Tage in Serie 5 in grösserer Häufigkeit vertreten sind als in Serie 2. Diese verhältnismässig kurzdauernden Symptome können indessen nicht die Unterschiede zwischen den Ergebnissen der beiden Serien im späteren Verlauf des letzten Tages erklären.

4) Dass schnell Gewöhnung eintritt, so dass die Vp. in Serie 5 auf die wiederholte Dosis des letzten Tages weniger reagieren. Deshalb könnte die Wirkung dieser Dosis — trotz der noch vom Vortage her andauernden Benzodrinwirkung — nicht grösser sein als die Wirkung derselben Dosis, wenn sie Serie 2 am letzten Tage erstmalig verabreicht wird. Indessen sprechen die Schriftumsangaben gegen die Wahrscheinlichkeit einer Gewöhnung bei kurzdauerndem therapeutischem oder sonstigem Gebrauch.

Andererseits haben jedoch Davidoff und Reifenstein 1937, sowie Jacobsen und seine Mitarbeiter, 1938, bei normalen Vp. während der ersten Experimentstage eine schwächere Wirkung gesehen. Wie aus dem oben Gesagten hervorgeht, können die Versuchsbedingungen zu einer scheinbaren Verminderung der Benzodrinwirkung beitragen.

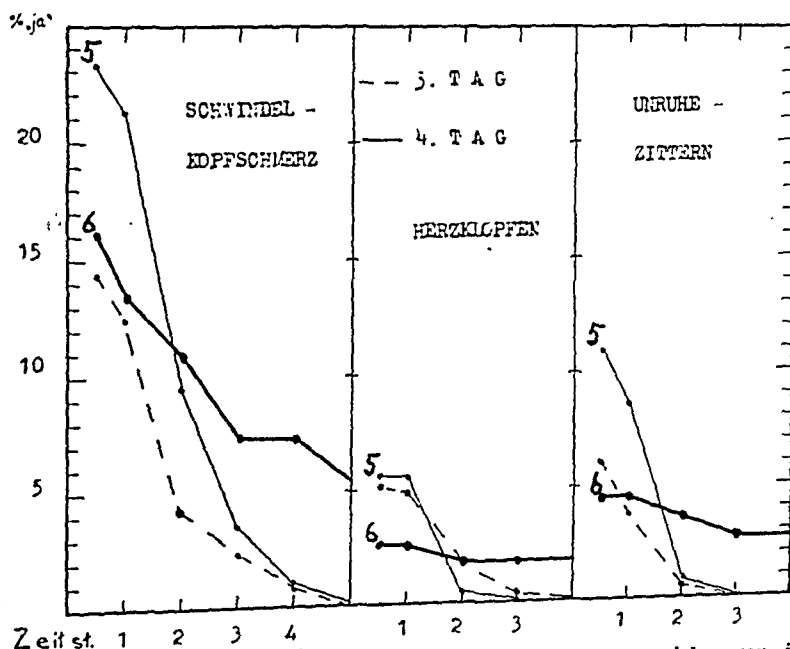
## 2. Ungünstige Nebenwirkungen.

Die Figuren 5 und 6 sowie die Tabellen 4 und 5 geben die Häufigkeit und Dauer der nachgefragten Nebenwirkungen Schwindel, Kopfschmerz, Herzklopfen und Unruhe-Zittern an.



Figur 5. Häufigkeit und Dauer der ungünstigen Nebenwirkungen am letzten Tage. Die Zahlen sind die Seriennummern. Die x-Achse gibt die Zeit in Stunden an, die y-Achse die Anzahl der Vp. in Prozent.

In erster Linie werden die Serien 1—4 abgehandelt. Die Anzahl der Vp., die subjektive Beschwerden irgendwelcher Art melden, ist in allen Serien ungefähr die gleiche, nämlich etwa 20 % (Tabelle 4). Wir finden (Figur 5, Tabelle 5) *Schwindel-Kopfschmerz* in 7—14 % der Bazedrin-Pervitin-Serien (16 % der Kontrollserie) während



Figur 6. Häufigkeit und Dauer der ungünstigen Nebenwirkungen in den Serien 5 und 6 am vorletzten (---) und letzten (—) Versuchstage. Die erstgenannten Kurven geben den Mittelwert der beiden Serien an. Die x-Achse gibt die Zeit die Stunden, die y-Achse die Anzahl der Vp. in Prozent an.

Tabelle 4.

Frequenz und Stärke der ungünstigen Nebenwirkungen am vorletzten und letzten Tage.

Versuchsserie	1.	2.	3.	4.	5.	6.
Anzahl der Vp. mit irgendwelchen Beschwerden am vorletzten Tage .....	—	—	—	—	23	19
am letzten Tage .....	23	24	20	21	16	20
Anzahl der Vp., die ihre Felddiensttauglichkeit für vorübergehend herabgesetzt hielten am vorletzten Tage .....	—	—	—	—	1.9	3.6
am letzten Tage .....	4.4	2.8	3.5	1.9	4.7	8.2

einer halben Stunde. Dann nimmt die Häufigkeit schnell ab. Mittlere Dauer 1—1.8 (2.8) Stunden. Die Beschwerden halten also in der Kontrollreihe länger an, was so zu erklären ist, dass Schwindel und Kopfschmerzen grossenteils auf die Ermüdung zurückzuführen sind; diese Beschwerden werden durch Benzodrin oder Pervitin behoben.

Die *Unruhe* und das *Zittern* haben eine mittlere Dauer von 1.5—1.7 (5) Stunden. Die Tabletten beheben somit in nicht geringem Umfang diese durch die Müdigkeit bedingten Beschwerden.

Das *Herzklopfen* dauert im Mittel 1—1.5 (2) Stunden an. Die Prozentsätze liegen hier in gewissen Benzodrin-Pervitin-Serien höher. Während einer halben Stunde 2.8—16 (3.5) % und während zwei Stunden 0.8—3.6 (2.6) %. Das Benzodrin ruft also bei einem gewissen Prozentsatz Herzklopfen hervor, doch ist diese Nebenwirkung von kurzer Dauer.

Bei der verabreichten Dosis und unter den vorliegenden Umständen spielt also nur das Herzklopfen als Nebenwirkung eine gewisse Rolle. Indessen sind diese Beschwerden von schnell vorübergehender Natur, und die in Serie 2 gefundenen hohen Werte dürften wenigstens teilweise durch Zufälligkeiten bedingt sein, auf die in Kap. II näher eingegangen wird.

Der Grad der in Rede stehenden Nebenwirkungen wird durch die Antworten auf die Frage beleuchtet, inwieweit die Beschwerden subjektiv vorübergehend die Felddienstfähigkeit herabgesetzt hätten, Tabelle 5. 1.9—2.8 (4.4) % haben diese Frage bejaht.

Tabelle 5.

Subjektiv ungünstige Wirkungen von 20 mg Benzedrin (Ser. 2), 30 mg Benzedrin (Ser. 3) und 18 mg Pervitin (Ser. 4), am letzten Tage des Dreinächteversuchs verabfolgt. Ausserdem werden die Werte der Serien 5 und 6 angeführt, die am vorletzten Versuchstage 20 mg Benzedrin bekamen, Ser. 5 ausserdem 20 mg am letzten Versuchstage. Für Ser. 2 werden die absoluten Werte aufgeführt, für die übrigen Serien die Abweichungen von diesen Werten. Die Tabelle will eine schematische Übersicht geben.

	Ser. 2. 20 mg Benz.	Kon- troll- serie	Änderung gegenüber Ser. 2.			
			4. Versuchstag			3. Ver- suchstag
			Ser. 3. 30 mg Benz.	Ser. 4. 18 mg Perv.	Ser. 5. 20 mg Benz.	Ser. 5. und 6. 20 mg Benz.
Schwindel-Kopfschmerz						
½ Stde. ....	14.0	+ 2.0	—7.0	—	+ 9.0	+ 0.5
1 " ....	11.0	+ 0.3	—6.5	— 0.5	+10.2	+ 1.5
2 Stdn. ....	5.0	+ 3.0	—4.1	— 1.6	+ 3.0	— 0.9
Herzklopfen						
½ Stde. ....	16.0	—12.5	—4.0	—13.2	—10.4	—11.0
1 " ....	11.1	— 7.5	—1.2	— 8.3	— 5.2	— 6.1
2 Stdn. ....	3.6	— 1	—2.8	— 2.8	— 3.6	— 1.8
Unruhe-Zittern						
½ Stde. ....	11.0	— 2.0	—1.0	— 2.0	+ 1.0	— 6.2
1 " ....	8.2	— 0.4	—1.2	— 3.0	+ 0.2	— 2.2
2 Stdn. ....	5.2	— 0.8	—2.7	— 2.4	— 4.3	— 4.5

Wie wir in einer folgenden Arbeit, Alwall, 1943, sehen werden, zeigen diejenigen, die am Morgen (vorübergehendes) Herzklopfen hatten, bessere Leistungen im Geländelauf später am Tage. Nach dem Abklingen dieser Überdosierungserscheinungen lag die verabfolgte Dosis für die betreffenden Versuchspersonen also näher der optimalen als für die übrigen.

Die Angaben über die Nebenwirkungen sind weniger nuanciert als in der Arbeit von Bahnsen, Jacobsen und Thesleff, 1938. Hier werden nur Angaben über die durchschnittliche Schlafzeit, 8.9 Stunden, nicht über etwaige sonstige Schlafstörungen gemacht. Die kürzere Schlafzeit einer gewissen Anzahl von Versuchspersonen nach Abschluss der Übungen kommt daher, dass einige jüngere

Offiziere die sportliche Leistung noch weiter treiben wollten und sich deshalb bis spätabends in geselligem Beisammensein wach hielten. Ausserdem darf man wohl mit der Möglichkeit rechnen, dass sich bei den Angaben über die Schlafzeit eine gewisse Prahlerei geltend gemacht hat. Bei der Inspektion der Mannschaftsräume um 21.30 Uhr lagen jedenfalls alle Versuchsteilnehmer in tiefem Schlafe und reagierten nicht, als Licht gemacht wurde, was die übrigen Insassen, die nicht an den Ermüdungsübungen teilgenommen hatten, taten. Die Schlafzeit war bis 8 Uhr morgens begrenzt.

Im Zweinächteversuch (siehe Alwall, 1943) gaben drei Teilnehmer der Benzedrinstrie (20 mg Benzedrin, etwa 240 Vp.) und ebenso viele der Kontrollserie (etwa dieselbe Anzahl) an, sie hätten schlecht einschlafen können.

Die Schlafstörungen, die nach denselben Dosen bei nicht ermüdeten Versuchspersonen auftreten (Jacobsen u. Mitarb.), dürften bei starker Ermüdung ausbleiben oder an Häufigkeit und Stärke nachlassen.

### 3. Besprechung der wichtigsten Versuchsergebnisse.

Nachstehend werden die wichtigsten Versuchsergebnisse in Anlehnung an einen Überblick über das Schrifttum erörtert.

#### a) Angenehme Wirkungen.

Bahnsen, Jacobsen und Thesleff legten 1938 die Ergebnisse einer umfassenden Untersuchung über die subjektiven Wirkungen des Benzedrins bei nicht ermüdeten Versuchspersonen vor und gaben eine eingehende Analyse des Materials. Ihre Arbeit ist grundlegend, und die folgenden Jahre haben zu den darin berührten Fragen nichts wesentlich Neues erbracht. Indessen sind diese Untersuchungen an Menschen ausgeführt, die ihrer üblichen beruflichen Arbeit nachgingen, ohne dass besondere Massnahmen zur Herbeiführung stärkerer Ermüdung getroffen wurden. Praktisch sämtliche übrigen einschlägigen Untersuchungen sind ebenfalls an wenig oder gar nicht ermüdeten Personen vorgenommen worden.

Jacobsen und seine Mitarbeiter untersuchten mittels Fragebogen das subjektive Befinden im Laufe des Tages teils bei etwa 200 Versuchspersonen, die keinerlei Tabletten bekamen, teils in zwei Reihen von je 100 Versuchspersonen, die morgens entweder Leertabletten oder 10 bzw. 20 mg Benzedrin (Frauen bzw. Männer) erhielten. Sie hatten so eine Normal-

gruppe (keine Tabletten), eine Kontrollgruppe (Leertabletten) und eine Benzodringruppe. Am Morgen des Versuchstages mussten die Versuchspersonen — im Alter von 17 bis über 50 J.; etwa die Hälfte waren Frauen — einen Fragebogen betreffend ihr subjektives Befinden ausfüllen, ferner mussten sie über ihren Schlaf während der folgenden Nacht Rechenschaft ablegen. In besonderen Serien untersuchten sie die Bedeutung der Instruktion bezüglich der vermutlichen Wirkungen, die den Versuchspersonen bei Ausgabe der Tabletten erteilt wurde. Die Ergebnisse waren bei neutraler und suggestiver Instruktion praktisch die gleichen.

Ein direkter Vergleich zwischen den Befunden Jacobsens und seiner Mitarbeiter einerseits und den hier vorgelegten andererseits verbietet sich aus folgenden Gründen:

1) die Vp. waren nicht ermüdet; 2) die Hälfte der Vp. waren Frauen; 3) die Frauen bekamen 10 mg, die Männer 20 mg Benzodrin; (Doch stellen B., J. und T. gewisse Angaben über die Versuche mit den Männern zusammen, weshalb doch ein gewisser direkter Vergleich möglich ist.) 4) unter den unangenehmen Nebenwirkungen geben sie auch die Schlafstörungen an.

Jacobsen und seine Mitarbeiter fanden eine überwiegend angenehme Gesamtwirkung in 28 %, eine indifferente (angenehm = unangenehm) in 35 %. Der Vergleich scheint mit der Summe dieser Zahlen, 63 %, vorzunehmen zu sein. In den hier vorgelegten Untersuchungen hatten 20 mg Benzodrin angenehme Wirkungen auf 93 % der Vp. nach 20 mg Benzodrin und 97 % nach 30 mg.

B., J. und T. finden in 19 % keinerlei Wirkungen, weder günstige noch ungünstige. In der vorliegenden Untersuchung fehlen günstige Wirkungen höchstens bei ein paar Prozent aller Versuchspersonen; die wenigsten »Versager« finden sich in den Serien mit 30 mg Benzodrin, ein wichtiger Befund. Man dürfte also vermuten können, dass praktisch alle irgendeine Wirkung — angenehme oder unangenehme — verspürt haben und dass bei individueller Dosierung in allen Fällen eine günstige Wirkung erzielt worden wäre.

Nathanson, 1937, befragte 55 normale Vp. über das subjektive Wohlbefinden nach dem Einnehmen von 20 mg Benzodrin. Das Benzodrin wurde entweder in zwei Dosen zu je 10 mg vor dem Frühstück und dem Mittagessen oder in einer Dosis von 20 mg vor dem Mittagessen genommen. Von den 25 Personen der Kontrollgruppe, die Leertabletten erhalten hatten, gaben 84 % keine Reaktion an; die übrigen Angaben beziehen sich auf nur eine

oder zwei Versuchspersonen (4—8 %), sind also unsicher. Die meisten Reaktionen waren  $\frac{1}{2}$ —1 Stunde nach Einnahme der Tabletten zu verzeichnen.

Eine eingehendere Analyse des Materials ist nicht durchgeführt worden. Die letzteren Zeitangaben werden ohne Detailangaben gemacht, weshalb kein kritischer Vergleich angestellt werden kann. Nathansons Angaben über die Reaktion seiner Versuchspersonen auf Benzedrin umfassen ausserdem auch Schlafstörungen.

Ranke, 1939, schreibt in seinem kurzen Autoreferat, auf das ich noch zurückkomme: »Bei Vagotonikern fehlt die günstige Wirkung.« Seifert, 1939, gab der halben Truppe, 10 Mann, vor einem Trainingsgepäckmarsch über 25 km 12 mg Pervitin. Von der behandelten Gruppe gaben 8 Mann an, dass sie sich auffallend frischer gefühlt hätten und die Stimmung besser war, was ihnen im Vergleich zu der früheren Märschen aufgefallen ist; die beiden übrigen hatten keine subjektiven Wirkungen verspürt. Der Zustand der nicht behandelten Marschteilnehmer wird im Vergleich zu früheren ähnlichen Märschen als unverändert bezeichnet; indessen fielen 5 Mann unterwegs aus, so dass die Kontrollgruppe nur 5 Mann umfasste. — Sonstiges Material wird nicht vorgelegt, weshalb die Angaben sich nicht kritisch beurteilen lassen: »Insgesamt ergaben die Untersuchungen an Gesunden, dass sich eine Wirksamkeit des Präparates in wenigstens 80 % der Fälle nachweisen liess. In etwa 15 % war ein Effekt nicht sicher festzustellen oder es trat nur ein leichter Unruhezustand mit Hitzegefühl ein; in 15 % der Fälle wirkte Pervitin ungünstig.« An anderer Stelle des Aufsatzes werden unangenehme Nebenwirkungen in 15 % angegeben.

Die in die Lehrbücher schon eingedrungene Angabe, nur etwa 30 % reagierten auf 10—20 mg Benzedrin günstig (durch verminderte Müdigkeit, gesteigerte Arbeitslust, gehobene Stimmung), kann also nicht als allgemein gültig angesehen werden.

Die Voraussetzung für einen günstigen Benzedrineffekt auf Stimmung und psychische Leistungsfähigkeit dürfte sein, 1) dass ein Ermüdungszustand o. dgl. vorliegt, der behoben werden kann, 2) dass die verabfolgte Dosis in der gegebenen Situation ausreichend gross ist, 3) dass andererseits die Dosis nicht so gross ist, dass die unangenehmen Wirkungen über die angenehmen hinausgehen und so einen weniger guten oder gar keinen günstigen Effekt vortäuschen, ja, dass sogar die Müdigkeit infolge gesteigerter psychischer Spannung o. dgl. zunimmt. Liegt bereits von vornherein eine nervöse Spannung, Gereiztheit o. dgl. vor, wodurch die Leistungs-

fähigkeit herabgesetzt wird, so dürfte dieser Zustand — wenigstens vorübergehend — auch durch eine geringe Menge Benzedrin oder Pervitin verschlimmert werden können; ein Sedativum dagegen könnte unter diesen Umständen von guter Wirkung sein. Die besagte Erscheinung hindert nicht, dass eine solche Vp. nach einigen Stunden — wenn sich die ungünstige Wirkung ausgeglichen hat — eine bessere psychische Leistungsfähigkeit und Ausdauer haben kann. Unerwünschte Nebenwirkungen können mit günstigem Effekt vereinbar sein. — 4) Eine unbedingte Voraussetzung für günstige Wirkung ist natürlich, dass die betreffende Person sich nicht schon im Zustand absoluter Erschöpfung befindet.

Bei stärkerer Ermüdung, wie in dem vorliegenden Material, hat man damit zu rechnen, dass zahlreiche, vielleicht sämtliche, Vp. günstig auf eine grössere Dosis reagieren, nur verhältnismässig wenige aber ungünstig. Auf dieselbe Dosis reagiert bei einem nicht-ermüdeten »Normalmaterial« ein Teil günstig, ein verhältnismässig grosser, überwiegender Teil ungünstig und schliesslich eine ganze Anzahl überhaupt nicht.

Die Grundregel für die Darreichung dieser Mittel zum Ziele besserer psychischer Leistung ist: möglichst kleine, bei Bedarf evtl. wiederholte Dosen.

Wie im folgenden dargelegt wird, kann sich eine gewisse Erfahrung bezüglich besserer Wirksamkeit des Pervitins möglicherweise so erklären, dass dieses Mittel in Tabletten zu 3 mg erhältlich ist, während Benzedrin in 5- und 10-mg-Tabletten zum Verkauf kommt. Die Dosierung ist gewöhnlich »eine Tablette«, wobei Benzedrin bei dem geringen Ermüdungsgrad, bei dem die Mittel gewöhnlich zur Anwendung kommen, oft überdosiert werden dürfte.

Was die physische Leistungsfähigkeit angeht, liegen die Dinge möglicherweise anders. Hier dürften in der Regel etwas grössere Dosen vonnöten sein, wobei etwa auftretende Überdosierungserscheinungen — wenigstens für den Augenblick — weniger erheblich sein werden. Hierauf komme ich noch zu sprechen (Alwall, 1943).

#### b). *Unangenehme Nebenwirkungen.*

Lemmel und Hartwig, 1940, sahen unangenehme Nebenwirkungen bei 30 % der Versuchspersonen nach 6 mg Pervitin und bei 18 % der Kontrollgruppe (nicht ermüdete Soldaten).



Jacobsen und seine Mitarbeiter stellten eine überwiegend unangenehme Gesamtwirkung in 28 % ihres Materials und indifferente (angenehm = unangenehm) in 35 %, also Nebenwirkungen in 53 % fest. Diese Zahlen lassen sich, wie schon dargelegt wurde, mit den hier vorgelegten nicht direkt vergleichen, da die genannten Autoren auch die Schlafstörungen zu diesen Nebenwirkungen rechnen. Doch ist es wahrscheinlich, dass Nebenwirkungen hier in bedeutend kleinerem Ausmass vorkommen.

Die Unterschiede dürften sich durch die verschiedenen Versuchsbedingungen erklären. Infolge der grossen Ermüdung sind durch Überdosierung bedingte Nebenwirkungen hier weniger wahrscheinlich. Bei Versuchen mit nicht ermüdeten Personen ruft die gleiche Menge in grösserem Ausmass Überdosierungserscheinungen hervor. Bei Übermüdeten wirkt Benzodrin sogar in gewissem Grade als Curativum für durch die Ermüdung verursachte »Nebenwirkungen«. Sowohl von den angenehmen als den unangenehmen Wirkungen des Benzodrins (und Pervitins) gilt also, dass diese nicht nur davon abhängig sind, wie der einzelne im allgemeinen reagiert, sondern hochgradig auch von der Dosierung und der augenblicklichen Disposition des Betreffenden.

### c) Die Wirkungsdauer.

In diesen Untersuchungen ist durch Detailstudien gezeigt worden, dass die Dauer der günstigen Wirkungen von 20 mg Benzodrin unter den hier gegebenen Versuchsbedingungen trotz der fortschreitenden starken Ermüdung sich über mindestens 36 Stunden erstreckt. Es dürfte klar sein, dass die Wirkungsdauer 1) von der zugeführten Dosis, 2) von der individuellen Empfindlichkeit und 3) von der zufälligen Disposition abhängig ist. Bei weniger ermüdeten Personen hält die Wirkung einer kleineren Dosis länger an, während bei stärkerer Ermüdung innerhalb kürzerer Zeit wiederholte relativ grosse Dosen verabreicht werden können.

Jacobsen und seine Mitarbeiter sahen bei 30 % ihrer Versuchspersonen Wirkungen (Schlafstörungen) noch nach 12—14 Stunden und bei 20 % (durch vorzeitiges Erwachen) gar noch nach 24 Stunden. Systematische Untersuchungen über die Wirkungsdauer haben sie sonst nicht angestellt. Doch gehen sie an, dass eine Umfrage bei einigen Versuchspersonen den Eindruck erweckt habe, dass sowohl günstige als ungünstige Wirkungen

tagelang andauern können. — Jacobsen und Gad, 1940, fanden nach einmaliger Darreichung von Benzedrin noch 3 Tage später Ausscheidung im Harn.

Nathanson bemisst die Wirkungskdauer von 20 mg Benzedrin auf 7—12 Stunden, ohne das Material vorzulegen, worauf er diese Schlussfolgerung stützt.

## Kap. II.

### Vergleich zwischen Benzedrin und Pervitin mit Rücksicht auf die subjektiven Wirkungen und Nebenwirkungen.

Die Serien 2 und 3 bekamen am Morgen des letzten Tages 20 bzw. 30 mg Benzedrin, während Serie 4 18 mg Pervitin bekam. Doch ist hier zu bemerken, dass die Versuchspersonen der Serie 2 die 20 mg Benzedrin auf einmal nach einer leichten Mahlzeit erhielten, während Serie 3 und 4 ihre Dosis zwar ebenfalls im Zusammenhang mit einer leichteren Mahlzeit bekamen, doch so, dass sie zunächst zwei Drittel und nach etwa einer halben Stunde das restliche Drittel einnehmen mussten. Durch diese Aufteilung wollte man die Unannehmlichkeiten vermeiden, die eine zu plötzliche Resorption einer grossen, auf einmal gegebenen Dosis mit sich bringen kann. Andererseits erschwert diese Art der Zuteilung den Vergleich zwischen den Serien 2 und 4 namentlich betreffs der Nebenwirkungen. Für die verabfolgte Pervitindosis entschied ich mich nach vorbereitenden Selbstversuchen.

Tabelle 3 vergleicht die *günstigen Wirkungen* von 20 mg Benzedrin in Serie 2 und die in den übrigen Serien, die am Morgen des letzten Tages Benzedrin oder Pervitin bekommen hatten. Für Serie 2 sind die absoluten Zahlen angegeben, für die Serien 3 und 4 die Abweichungen der betreffenden Prozentzahlen von denjenigen in Serie 2.

Verglichen werden die Wirkungen von etwa gleich grossen (d.h. 20 und 18 mg) Mengen Benzedrin und Pervitin sowie einer grösseren Benzedrinmenge (30 mg). Die Voraussetzung dafür, dass ein Vergleich unter den gegebenen Bedingungen erfolgen kann, ist die, dass die grössere Benzedrindosis einen besseren Effekt hervorruft als die kleinere.

Die Antworten auf die Fragen nach günstigen Wirkungen überhaupt, die die Teilnehmer im Laufe des Tages verspürten, sind in Fig. 4 und Tabelle 3 wiedergegeben. 30 mg Benzedrin wirkten besser als 20 mg, und 18 mg Pervitin wirkten erheblich schwächer. Die Frequenz der Wirkungen »entschiedener Nutzen der Tab-

letten» und »gehobene Stimmung» ist in den drei Serien von gleicher Grössenordnung.

Im Geländelauf (A. 1943) hat Serie 3 den besten Durchschnittswert, gefolgt von Serie 2, während Serie 4 an letzter Stelle steht.

Wir finden somit eine überwiegend stärkere günstige Gesamtwirkung von 30 als von 20 mg Benzodrin. 18 mg Pervitin wirkt in wesentlichen Punkten schlechter als 20 mg Benzodrin.

Diese Befunde schliessen nicht die Möglichkeit aus, dass Pervitin doch eine grössere Wirkungsstärke als Benzodrin haben könnte. Wenn dies der Fall wäre und Überdosierung in grösserem Ausmass vorkäme, könnten die ungünstigen Wirkungen in gewissem Umfang überwiegen und die günstigen verdecken; ich verweise diesbezüglich auf die Diskussion in Kap. I. Wie aus dem folgenden hervorgeht, sind indessen die nach der hier angewandten Pervitindosis auftretenden unerwünschten Nebenwirkungen eher geringer. — Da die Nebenwirkungen nach 30 mg Benzodrin nicht stärker und zahlreicher sind als nach 20 mg, dürften auch die Werte in Serie 3 eine zuverlässige Vergleichsbasis darstellen.

*Die Wirkungsstärke von 18 mg Pervitin ist bei diesen ermüdeten Versuchspersonen also nicht grösser, sondern wahrscheinlich geringer als die von 20 mg Benzodrin. Die Befunde sprechen somit auch gegen die Richtigkeit der im Schrifttum bezeugenden Angaben, Pervitin sei wirksamer als Benzodrin.*

Tabelle 5 gibt eine Übersicht über die entsprechenden Unterschiede, die zwischen Serie 2 und den übrigen hinsichtlich der *ungünstigen Nebenwirkungen* bestehen. Diese Nebenwirkungen sind in Kap. I abgehandelt worden. Die Gesamtzahl der Versuchspersonen, die Nebenwirkungen gemeldet haben, ist in den Serien 1—4 die gleiche; ebenso liegen keine sicheren Unterschiede in der Anzahl derjenigen vor, die ihre Felddiensttauglichkeit als durch die Beschwerden herabgesetzt betrachteten (Tabelle 4).

Serie 3 hat bedeutend niedrigere Werte für Schwindel und Kopfschmerz, und dies besagt, dass 30 mg Benzodrin als Curativum gegen dieses Müdigkeitssymptom gewirkt hat; 20 mg Benzodrin und 18 mg Pervitin sind offenbar nicht so effektiv, verursachen anscheinend aber auch nicht die genannten Nebenwirkungen. Trotz der kleinen Zahlen darf man möglicherweise vermuten, dass 30 mg Benzodrin stärker wirksam ist als die beiden übrigen Dosen.

Unruhe und Zittern kommen in den Serien 1 und 2 in etwa der-

selben Häufigkeit vor, in den übrigen Serien etwas weniger oft, so dass möglicherweise das Präparat in diesen letzteren die fraglichen Beschwerden vermindert hat.

Wie schon in Kap. I dargelegt, wurde Herzklopfen in Serie 2 bemerkenswert oft gemeldet, und zwar liegen die Werte dieser Serie sowohl über denen der Kontrollserie als auch denen der Serie 3 mit der höheren Benzedrindosis. Am niedrigsten ist die Frequenz dieses Symptoms nach 18 mg Pervitin in Serie 4, die etwa die gleichen Werte wie die Kontrollserie (Serie 1) hat. Diese Befunde rechtfertigen jedoch nicht ohne weiteres die Schlussfolgerung, dass Pervitin weniger oft Herzklopfen verursache als Benzedrin.

Die Dosis von 18 mg Pervitin ist ebenso wie 30 mg Benzedrin in  $\frac{2}{3} + \frac{1}{3}$  aufgeteilt und mit einem Intervall von etwa  $\frac{1}{2}$  Stunde einverleibt worden; wahrscheinlich war deshalb das Risiko von unangenehmen Wirkungen bei 20 mg Benzedrin grösser als bei dem Pervitin.

Folgende Umstände sprechen dafür, dass die hohe Frequenz des Herzklopfens in Serie 2 durch Zufälligkeiten bedingt war: 1) 30 mg Benzedrin ruft Herzklopfen in niedrigerer Frequenz hervor als 20 mg. 2) In den Serien 5 und 6, die am 3. Versuchstage 20 mg Benzedrin bekommen haben, tritt Herzklopfen an diesem Tage nur in geringem Ausmass ein. Die Wahrscheinlichkeit spricht dafür, dass Nebenwirkungen nach gleicher Dosis bei weniger starker Ermüdung in grösserem Ausmass hätten auftreten müssen (siehe Kap. I).

Ad. 1.: Doch ist vielleicht eine Verdeckung des subjektiven Herzklopfens durch die stärkere Euphorie u.s.w. nach der grössten Benzedrindosis möglich.

*Wenn auch die Möglichkeit nicht ausgeschlossen ist, dass Benzedrin in grösserem Umfang kurzdauerndes Herzklopfen verursacht als Pervitin, spricht doch eine gewisse Wahrscheinlichkeit dafür, dass dies nicht der Fall ist.*

Soweit ich gefunden habe, dürfte dies die erste systematische Untersuchung sein, die einen Vergleich zwischen der Wirkungsstärke von Benzedrin und Pervitin am Menschen erlaubt.

Im Anschluss an die Schilderung gewisser tierexperimenteller Untersuchungen über die Wirkungen verschiedener Amine schreibt Hauschild, 1938, ohne experimentelle Daten anzuführen, folgendes: »Eine Bestätigung unserer tierexperimentellen Befunde ergaben die Versuche am Men-

schen. Die Dosierung des — (Pervitins) liegt *wesentlich niedriger*. Nebenwirkungen werden nur selten beobachtet. 3—6 mg üben schon kräftige Wirkungen aus, während — (Benzedrin) — auch nach Angaben in der Literatur *wesentlich höher dosiert werden muss.*»

Aus Frankes, 1938, Blutdruckstudien lässt sich kein sicherer Vergleich zwischen Benzedrin und Pervitin ablesen. Es heisst dort, dass »kleine Dosen«, bis 10 mg, keine Blutdrucksteigerung machen, grössere Dosen, etwa 20 mg über 5—7 Stunden hinaus blutdruckwirksam sind. 6 mg Pervitin bewirkten in der Hälfte der Fälle eine leichte Blutdrucksteigerung. Die Blutdrucksteigerung wird deutlicher nach 15 mg. Die Benzedrindosis für Blutdruckerhöhung liegt aber *wesentlich höher* als die für die psychische Stimulation geeignete Dosis; ausgesprochene Nebenwirkungen traten nach 20 mg auf. Beim Pervitin (höchstens 15 mg!) liegen die Dinge ähnlich; doch wird nur über die angenehmen Wirkungen berichtet.

Frankes Material umfasst für Benzedrin 8 und für Pervitin 30 Patienten mit Kreisläufstörungen (jugendliche und alte Hypotoniker). Die beiden Gruppen sind also verschieden gross und inhomogen, weshalb ein Vergleich zwischen Benzedrin- und Pervitinwirkung nicht möglich sein dürfte.

*Die in der Literatur vorliegenden Mitteilungen scheinen keine Möglichkeiten einer kritischen Beurteilung der Wirkungsstärke von Benzedrin und Pervitin im Verhältnis zueinander zu bieten.*

Beiläufig sei bemerkt, dass im praktischen Gebrauch, namentlich bei Benzedrin, eine Überdosierung zweifellos häufig vorkommt. Während Pervitin in Tabletten von 3 mg erhältlich ist, enthalten die Benzedrintabletten 3 oder 10 mg. Die Dosierung erfolgt oft ohne genaueres Nachdenken in »Tabletten«. Häufig dürften 3 mg Substanz oder weniger zur Erzielung der optimalen Wirkung genügen. Gibt man unter solchen Umständen eine Tablette von 5 oder 10 mg Benzedrin, so ist die Wirkung nicht besser, wohl aber treten oft mehr störende Nebenwirkungen auf.

### Zusammenfassung.

Es ist untersucht worden, wie Benzedrin und Pervitin auf etwa 700 Versuchspersonen einwirken, die vorher in 3 aufeinander folgenden Nächten sowie an den Zwischentagen durch anstrengende Übungen fast ohne Schlaf in einen Zustand starker Ermüdung gebracht worden waren. Während die Kontrollserien Leertabletten bekamen, erhielten die übrigen 20 oder 30 mg Benzedrin oder 18 mg Pervitin. Die Tabletten wurden in allen Serien am Morgen letzten Tages ausgegeben, sowie in zwei von den sechs Versuchs-

serien ausserdem am Morgen des vorletzten Tages. Durch Erfragung des subjektiven Befindens ist in den einzelnen Versuchsreihen die Anzahl derjenigen ermittelt worden, die mit günstigen Wirkungen bzw. ungünstigen Nebenwirkungen reagiert haben. Auch die Wirkungsdauer der verabfolgten Stoffe ist bestimmt worden.

Im Kontrollmaterial lässt die am frühen Morgen herrschende Müdigkeit im Laufe des Tages spontan nach, was u. a. auf dem Wechsel von Müdigkeit und Wachen im normalen Tagesrhythmus beruht. Die Müdigkeit ruft verschiedene subjektive Beschwerden hervor.

Benzedrin und Pervitin beheben oder vermindern die subjektiven Müdigkeitserscheinungen und heben die Stimmung. Praktisch sämtliche Versuchspersonen reagieren günstig; die Zahlen der vorliegenden Untersuchung übersteigen bei weitem die sonst im Schrifttum genannten. Die früheren einschlägigen Untersuchungen haben mit wenig oder gar nicht ermüdeten Versuchspersonen gearbeitet, wodurch sich der Unterschied der Befunde erklären dürfte. Die frühere Annahme, dass viele Menschen auf Benzedrin oder Pervitin nicht günstig oder überhaupt nicht reagieren, trifft nicht zu.

In der Besprechung der Befunde wird dargetan, dass die Voraussetzung für eine günstige Wirkung darin liegt, dass ein Ermüdungszustand o. dgl. vorhanden ist, der behoben werden kann, dass die Dosierung ausreichend ist, dass nicht Überdosierung unerwünschte Nebenwirkungen in solcher Stärke hervorruft, dass der günstige Effekt dadurch verdeckt wird, und dass der Betreffende nicht so erschöpft sein darf, dass die Bedingungen einer günstigen Reaktion nicht mehr gegeben sind. Wenn also die Voraussetzungen für eine günstige Wirkung vorhanden sind und die passende Dosierung gewählt wird, dürfte man praktisch stets mit einer solchen Wirkung von Benzedrin und Pervitin rechnen können.

Es ist erstmalig gezeigt worden, dass der günstige Effekt von 20 mg Benzedrin trotz fortschreitender, hochgradiger Ermüdung mindestens 36 Stunden andauert.

In der Diskussion wird hervorgehoben, dass die Wirkung einer kleinen Dosis bei leichter Ermüdung bedeutend länger anhalten dürfte als bei starker Ermüdung.

Erstmalig ist die Dauer der unerwünschten Nebenwirkungen eingehend untersucht worden. Es zeigt sich, dass die Nebenwirkungen hier von kurzer Dauer und geringer Häufigkeit sind, ja, in ge-

wissen Fällen in geringerem Ausmass auftreten als in den Kontrollserien, woraus hervorgeht, dass die zugeführten Stoffe gewisse Ermüdungserscheinungen beheben. Nach den Schrifttumsangaben ist es wahrscheinlich, dass bei gleicher Dosis Nebenwirkungen in bedeutend grösserem Umfang an nicht ermüdeten Versuchspersonen beobachtet werden. Dies erscheint als eine natürliche Folge des oben Gesagten: bei geringerer Ermüdung bedarf es einer niedrigeren Dosis; die Grenze der Überdosierung liegt dann auch tiefer als bei starker Ermüdung.

Ein Vergleich zwischen Benzodrin und Pervitin mit Rücksicht auf die subjektiven Wirkungen gab folgendes Resultat: Die subjektiv günstigen Wirkungen von 18 mg Pervitin sind nicht stärker, sondern wahrscheinlich schwächer als die von 20 mg Benzodrin; der Effekt von 30 mg Benzodrin ist stärker als bei den vorgenannten Dosen. Die Befunde sprechen also gegen die üblichen Angaben, das Pervitin sei wirksamer — in der Regel gibt man doppelte Wirkungsstärke an — als Benzodrin, welche Angaben auch durch das frühere einschlägige Schrifttum nicht bestätigt zu sein scheinen.

Unangenehme subjektive Nebenwirkungen traten in der Regel nach 20 oder 30 mg Benzodrin oder 18 mg Pervitin nicht in grösserem Umfang auf als in der Kontrollgruppe, die Leertabletten bekommen hatte. Gewisse Müdigkeitsbeschwerden werden durch die Präparate gemildert. Zwar lässt sich nicht ausschliessen, dass Benzodrin in grösserem Umfang Herzklopfen verursacht als Pervitin, doch spricht eine gewisse Wahrscheinlichkeit dafür, dass dies nicht der Fall ist.

Der Verf. weist auf die Möglichkeit hin, dass die allgemeine Ansicht, dass Pervitin »angenehmer«, »besser« wirke, ihren Grund darin hat, dass infolge der üblichen Tablettenstärke gewöhnlich Benzodrin in höherer Dosis gegeben und überdosiert wird.

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## Studien über die Einwirkung von Benzedrin und Pervitin auf die physische und psychische Leistungsfähigkeit hochgradig ermüdeter Menschen.

Von

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Hier werden Studien über die Wirkungen von Benzedrin und Pervitin auf die körperliche Leistungsfähigkeit und die psychischen Funktionen hochgradig ermüdeter Menschen vorgelegt. Das Schrifttum umfasst nur Versuche über die Wirkung der erwähnten Substanzen auf nicht- oder wenig-ermüdete Personen.

Planung der Versuche.

Die Ermüdung.

I. Studien über die Einwirkung von Benzedrin und Pervitin auf die körperliche Leistungsfähigkeit ermüdeter Menschen.

II. Studien über die Einwirkung von Benzedrin und Pervitin auf die psychische Leistungsfähigkeit. Die Bedeutung des Ermüdungsgrades für die Wirkung (Dosierung) des Benzedrins.

III. Studien über die Einwirkung von Benzedrin auf die Treffsicherheit ermüdeter Schützen beim Scheibenschiessen.

*Planung der Versuche.*

In Massenversuchen wurden junge, wohltrainierte, gesunde Männer (Soldaten), hauptsächlich im Alter von 20 bis 22 Jahren, durch anhaltende,

mehrere Tage und Nächte während körperliche Anstrengungen ohne Gelegenheit zum Schlafen in Zustand starker Ermüdung versetzt. Am ersten Tage, unmittelbar vor Beginn der Ermüdungsübungen, wurde die individuelle Leistungsfähigkeit durch gewisse Proben (Geländelauf, Scheibenschiessen usw.) ermittelt. Am letzten Morgen, unmittelbar nach Beendigung der Märsche und Übungen, wurden psychotechnische Proben gemacht. Danach wurden die Tabletten verteilt. (Scheintabletten bzw. Benzedrin- oder Pervitintabletten). Die volle Wirkung von den zugeführten Benzedrin- und Pervitindosen beginnt schon nach etwa  $\frac{1}{2}$  Stunde und dauert mehrere Stunden. Etwa 2 Stunden später wurden die psychotechnischen Proben wiederholt. Darauf folgten die übrigen Proben: Geländelauf und Scheibenschiessen.

In den Kontrollserien, die wirkungslose Scheintabletten bekamen, zeigt der Unterschied zwischen den Prüfungsergebnissen des ersten und des letzten Tages den Einfluss der Ermüdung und sonstiger Faktoren auf die Leistungsfähigkeit. Umfassen die Kontroll- bzw. die Benzedrin- und Pervitinserien — wie es hier der Fall ist — genügend viel Personen, so kann man, indem man die Summe der individuellen Unterschiede in den betreffenden Serien vergleicht, einen Gradmesser für die Wirksamkeit des Benzedrins und Pervitins zur Behebung der Ermüdungserscheinungen gewinnen.

Die Versuche wurden in drei verschiedenen Untersuchungsreihen bei verschiedenen Truppenteilen durchgeführt. 1) Daueranstrengung während zweier Nächte und am Zwischentage ohne Schlaf. Etwa 500 Teilnehmer, auf zwei gleich grosse Serien verteilt, von denen die eine am Morgen des letzten Tages 20 mg Benzedrin und die andere Scheintabletten bekam. 2) Daueranstrengung während dreier Nächte und an den Zwischentagen ohne Schlaf. Etwa 720 Mann wurden auf sechs Versuchsserien verteilt, die zu verschiedenen Zeitpunkten während der Übungen Benzedrin, Pervitin oder Scheintabletten bekamen.

Betreffs der Verteilung der Tabletten siehe Allwall, 1943, sowie Tabelle 2. 3) Daueranstrengung während  $1\frac{1}{2}$  bzw. 2 Nächte und am Zwischentag zwecks Feststellung der Benzedrinwirkung zu verschiedenen Tageszeiten. Etwa 200 Versuchsteilnehmer.

Sämtliche Versuchspersonen wurden im voraus über den Sinn der Versuche unterrichtet, doch so, dass keine Einzelheiten (das Vorkommen von Scheintabletten usw.) berührt wurden, die auf den Ausgang der Versuche von Einfluss hätten sein können.

### *Die Ermüdung.*

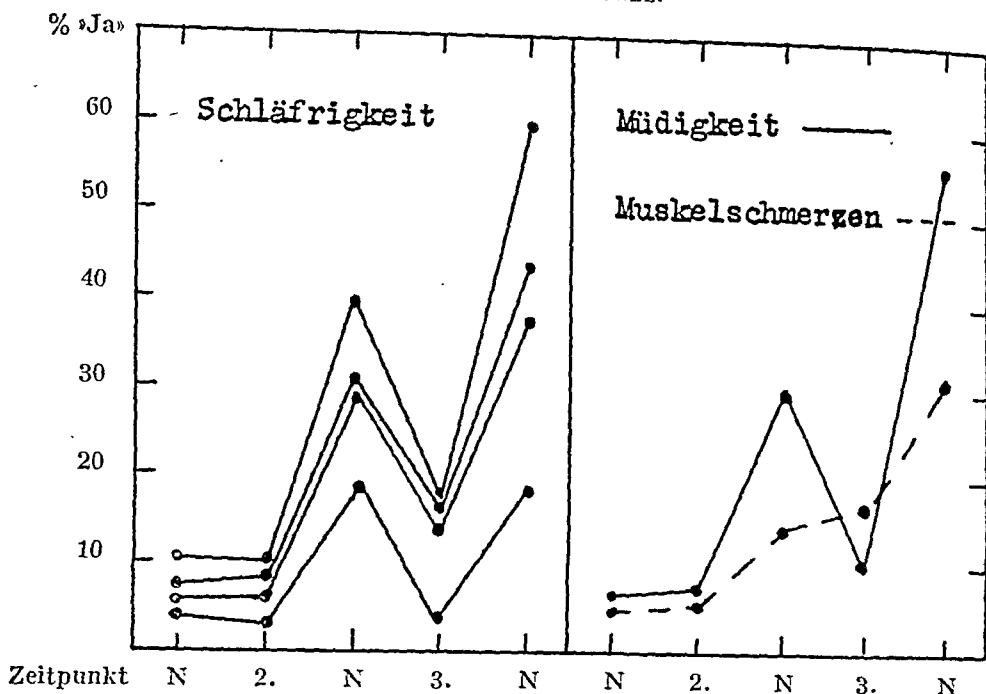
Im folgenden wird über einige Eindrücke von der fortschreitenden, hochgradigen Ermüdung bei den Versuchen berichtet, die sich über drei Nächte und die beiden dazwischenliegenden Tage erstreckten, ohne dass die Versuchsteilnehmer während dieser Zeit nennenswert zum Schlafen kamen.

Die Übungen wurden an einem Montag begonnen. Am Montag und Donnerstag wurden die vorerwähnten Proben angestellt. Von Montag abend 21 Uhr bis Donnerstag früh 4.30 Uhr wurde eine zusammenhängende doppel-seitige Übung durchgeführt, die den Teilnehmern möglichst kleine Gelegen-heit zu Schlaf oder Ruhe liess. Die einzigen Unterbrechungen waren täglich 2 Stunden Mittagspause und etwa gleich lange Zeit vor dem letzten Nachtmarsch zum Trocknen der Ausrüstung. In jeder der 3 Nächte wurde ein Marsch von 30 km gemacht, zum Teil auf schlechteren Wegen, ver-bunden mit Spähunternehmen und Wachdienst. Während der Gefechts-übungen am Tage wurden durchschnittlich etwa 15 km zurückgelegt, von den Spähtrupps bedeutend mehr. Die Gesamtmarschleistung betrug während der ganzen Übung im Durchschnitt etwa 125 km. Das Gelände war, von den Wegen abgesehen, mittelschwer, teilweise sumpfig. Es herrschte eine Temperatur von etwa  $+5^{\circ}$ , in der ersten Nacht fiel leichter Regen, im übrigen war das Wetter neblig. Das Marschgepäck wog zusammen etwa 22 kg. Von der teilnehmenden Truppe in einer Stärke von etwas über 1000 Mann wurden 720 zu den Tablettenversuchen herangezogen. Die Verpfle-gung war reichlich.

Da die Teilnehmer in der Nacht zum Montag in grossem Um-fang Urlaub gehabt hatten, wurden sie über die Dauer des Schlafes in der betr. Nacht befragt: durchschnittlich 6.1 Stunden. Durch-schnittlich wurden von den Teilnehmern 3.2 Stunden Schlaf ins-gesamt während der Übungen, von Montag bis Donnerstag mor-gen, angegeben. Es ist zu bemerken, dass dieser Schlaf bei kurzen Rastaufenthalten im Freien und bei kühler und unfreundlicher Wit-terung genossen wurde. Diese Angaben stehen in gutem Einklang mit den Berechnungen der Führung.

Die Länge der Nachtruhe nach Abschluss der Dreinächteübun-gen war durchschnittlich 8.9 Stunden. 5 % schiefen weniger als 8 Stunden. Diese Zeiten sind durch zwei Momente beeinflusst und zwar 1) die während der Nacht und auch am folgenden Tage noch fortdauernde Benzedrin- und Pervitinwirkung, die das Schlafbe-dürfnis und das Gefühl der Müdigkeit verringert, 2) das Wecken um 8 Uhr morgens. Ein Vergleich der in den verschiedenen Ver-suchsreihen ermittelten Schlafzeiten untereinander lässt keine sicheren Unterschiede erkennen.

Es waren besondere Vorkehrungen getroffen worden, um zu verhindern, dass jemand im Gelände zurückblieb. Um das Risiko des Einschlafens zu vermindern, wurde nachts immer 35 Minuten lang marschiert und 10 Minu-ten lang Rast gemacht. Die Nächte, besonders die zweite, waren schwer. Doppelsehen und Halluzinationen kamen vor. In der letzten Nacht wirkte



Figur 1.

a) Angaben über die Schläfrigkeit im Verlauf der Dreinächteübungen. Die obere Kurve zeigt die Anzahl der »sehr schläfrigen« an, die folgenden die Anzahl derjenigen, die »nur schwer wach bleiben« konnten, derjenigen, »die bei den Pausen in den Übungen einschliefen«, die untere Kurve schliesslich die Anzahl derjenigen, die »nach kürzeren Ruhepausen bei den Übungen geweckt werden mussten«. Die x-Achse gibt den Zeitpunkt an: die Nacht vor dem 2. Übungstag, den 2. Übungstag usw.; die y-Achse die Anzahl der Vp in Prozent.

b) Angaben über Müdigkeit und Muskelschmerzen.

zweifelloos das Bewusstsein, dass die Anstrengungen bald überstanden sein würden belebend.

Von über 1000 Übungsteilnehmern wurden 13 wegen Fusschaden, 6 wegen Erkältung nach Hause geschickt, 5 weitere wegen allgemeiner Ermüdung, welche letztere das Revier am Tage darauf verlassen konnten. Ernstere Krankheitsfälle sind nicht vorgekommen.

Figur 1 zeigt, dass die nachgefragten Ermüdungserscheinungen während der ersten 24 Stunden wenig ausgeprägt sind, im Laufe der zweiten Nacht stark zunehmen, um am dritten Tage wieder abzunehmen. Dies dürfte daran liegen, dass die Müdigkeit am Tage auch bei längerer Schlaflosigkeit weniger ausgeprägt ist. In der letzten Nacht hat die Anzahl derjenigen, die Ermüdung melden, weiter stark zugenommen. Die Häufigkeit der schmerzhaft betonten Erlebnisse, der Muskelschmerzen, nimmt in gleichmässiger ansteigender Kurve ohne derartige Schwankungen zwischen Tag und Nacht zu.

Im Anschluss an die obigen Versuchsergebnisse sei aus dem Schrifttum folgendes referiert.

Kleitman gibt in seiner Monographie über den Schlaf eine Übersicht über die Reaktion bei längerer freiwilliger Schlaflosigkeit. Er stützt sich auf die Erfahrungen aus jahrzehntelangen Versuchen an 35 Versuchspersonen. Um der Müdigkeit Herr zu werden, liess er die Versuchspersonen irgendeine Muskelarbeit ausführen, und wenn es nur Sprechen war. In der ersten Nacht war die Müdigkeit nicht besonders stark, abgesehen von einer vorübergehenden Schläfrigkeit zwischen 3 und 6 Uhr früh. Am folgenden Tage fühlten sich die Versuchspersonen ungefähr wie normal, nur war das Allgemeinbefinden weniger gut. Bei der gewohnten Tagesarbeit konnte die schlaflose Nacht fast vergessen werden, bei Untätigkeit aber machte sich die Schläfrigkeit bemerkbar. — Die zweite Nacht war von der ersten ganz verschieden. Die Augen brannten, und dieses Gefühl verschwand nur, wenn man die Augen schloss; schloss man aber die Augen, so drohte einen sofort der Schlaf zu übermannen. Selbst bei Spazierengehen war es schwer, sich wach zu erhalten. Lesen oder Studieren war unmöglich. Während 2—3 Stunden gegen Morgen wurde das Schlafbedürfnis fast übermächtig und Doppelsehen war häufig.

Später am Morgen liess die Schläfrigkeit wieder nach, und die Versuchspersonen konnten die gewohnte Arbeit im Laboratorium ungefähr wie sonst ausführen. Sie konnten sich nicht hinsetzen, ohne dass sie Gefahr liefen, einzuschlafen.

Die dritte Nacht glich der zweiten und der vierte Tag dem dritten.

Die hier mitgeteilten Versuche sind anderer Art als Kleitmans Observationen über die individuellen Reaktionen einer kleineren Anzahl von Versuchspersonen bei Ermüdung. Hier kommt nur die Anzahl derer zum Vorschein, die sich zur Zeit der Befragung, nämlich mitten am Tage sowie in der Morgendämmerung, sehr erschöpft fühlten usw. Gewisse Vergleiche sind jedoch möglich: In Übereinstimmung mit Kleitman finde ich die Symptome lästige Schläfrigkeit und körperliche Müdigkeit nachts stärker ausgeprägt als am Tage.

Ganz kurz sei hier die Einteilung der Übungen bei den Versuchen mitgeteilt, die sich über 2 Nächte und den dazwischenliegenden sowie den vorangehenden und den folgenden Tag erstreckten. Nach Beendigung der verschiedenen Proben am ersten Tage traten die Versuchspersonen abends zu einem Nachtmarsch über eine Strecke von etwa 30 km an. Unterwegs wurden Pausen für Übungen im Stehen eingelegt. Die Teilnehmer bekamen keine Gelegenheit zu schlafen. In der zweiten Nacht wiederholte sich das Programm der ersten. An dem dazwischenliegenden Tage wurden die Versuchspersonen mit Übungen verschiedener Art beschäftigt. Nur bei den Mahlzeiten wurde ihnen eine kurze Ruhe gewährt, doch kein eigent-

licher Schlaf. Die eine Hälfte der Versuchspersonen beendete die Übungen um 3 Uhr morgens, worauf die psychotechnischen Tests usw. durchgeführt wurden. Die andere Hälfte setzte die Übungen bis 6 Uhr früh fort.

## Kap. I. Einwirkung von Benzedrin und Pervitin auf die körperliche Leistungsfähigkeit ermüdeter Menschen.

Geländelauf: 3 km auf abgesteckter, leichter Bahn. Der erste Lauf wurde am ersten Tage, vor dem Beginn der Ermüdungsübungen, durchgeführt, der zweite am letzten Tage, etwa 2 ½—5 Stunden nach Einnahme der Tabletten, also bald nach dem Abschluss der Anstrengungsübungen. Vor dem letzten Lauf wurden die Vp. ausgeschieden, die wegen schwererer Fusschäden den Lauf nicht durchführen konnten bzw. erheblich behindert waren. Die Laufzeit wurde abgestoppt und aufgeschrieben. Der Unterschied zwischen der im ersten und im zweiten Lauf der Kontrollserie (Scheintabletten) erzielten Zeit ist durch Ermüdung und Faktoren zufälliger Art bedingt. Bei Vergleichung der Summe dieser individuellen Unterschiede in der Kontrollserie mit den Summen dieser Unterschiede in den übrigen Versuchsreihen erhält man ein Mass für die Einwirkung der untersuchten Stoffe auf die Leistungsfähigkeit ermüdeter Vp.

Die Wirkung von 20 mg Benzedrin im *Zweinächteversuch* ist aus Tabelle 1 zu ersehen. Während die Kontrollserie ihre Leistung verschlechtert, indem sie durchschnittlich im zweiten Lauf 95 Sek. langsamer läuft, verbessert die Benzedrinserie ihre Zeit mit 18 Sek. Eine bedeutend grössere Zahl von Vp. verbessert in der Benzedrinserie das individuelle Resultat. Der Unterschied ist signifikant.

71 Vp., die auf Befragen 2 Stunden nach Einnahme der Tabletten angaben, subjektives Unbehagen zu empfinden, verbesserten ihre Leistungen mehr als die übrigen Vp. der Benzedrinserie. Die Erklärung dürfte die sein, dass die betreffenden Vp. empfänglicher für Benzedrin, waren, so dass die verabfolgte Dosis für sie nahe der oberen therapeutischen Grenze lag. Die dabei auftretenden Beschwerden — die, wie in anderem Zusammenhang gezeigt wird, bald wieder verschwinden — beeinträchtigen die körperliche Leistungsfähigkeit nicht, ermöglichen vielmehr eine bessere Ausnützung der Kraftreserven.

*Eine Dosis von 20 mg Benzedrin erhöht also die körperliche Leistungsfähigkeit dieser ermüdeten Vp. Die subjektiven Nebenwirkungen beeinträchtigen das Ergebnis nicht.*

Die Ergebnisse des *Dreinächteversuchs*, über dessen Ermüdungsübungen bereits berichtet ist, sind in Tabelle 2 zusammengestellt.

Tabelle 1.

Die Einwirkung von Benzodrin auf die Leistung im Geländelauf über 3 km nach Ermüdungsübungen während zweier Nächte und am Zwischentage. In der Tabelle sind nur die Ergebnisse derjenigen Versuchspersonen angegeben, die bei der Befragung 2 Stunden nach dem Einnehmen des Benzodrins, also vor Beginn des Geländelaufs, irgendwelche ungünstigen Nebenwirkungen gemeldet hatten.

Versuchsserie	Leertabl.	20 mg Benzodrin	
		Sämtl. Teilnehmer	Nebenwirkungen
<i>1. Lauf</i>			
Mittelwert in Min. ....	18.01	18.06	
<i>2. Lauf</i>			
Bessere Zeit: Unterschied in Sek.			
gegenüber 1. Lauf ....	—7360	—16520	—5040
Anzahl d. Vp. ....	59	125	39
Unveränderte Zeit: (—30— + 30 Sek.)			
Anzahl d. Vp. ....	40	58	21
Schlechtere Zeit: Unterschied in Sek.			
gegenüber 1. Lauf ....	+28140	+12180	+1400
Anzahl d. Vp. ....	121	60	11
Ergebnis: Gesamtveränderung in Sek. ..	+20780	—4340	—3640
Anzahl d. Vp. ....	220	243	71
Medium, Sek. ....	+95 ± 13	—18 ± 11	—51 ± 14

Betreffs der Verteilung der Tabletten siehe Tabelle 2 sowie Alwall, 1943. Die im ersten Lauf erzielte Durchschnittszeit war etwas schlechter als im Zweinächteversuch. Verglichen werden hier nur die Ergebnisse der Ser. 1 (Kontrollserie.) mit den Serien 2—4, deren Vp. 20 bzw. 30 mg Benzodrin bzw. 18 mg Pervitin bekommen haben. Die Benzodrin- und Pervitinserien zeigen bessere Ergebnisse als die Kontrollserie und der Unterschied ist signifikant.

Die Unterschiede zwischen den Serien 2—4 unter sich werden bei der Besprechung der Wirkung von Benzodrin und Pervitin im Verhältnis zueinander abgehandelt werden (Alwall, 1943).

Die Streuung ist hier bedeutend grösser als im Zweinächteversuch, was — von der verschiedenen Grösse der Gruppen abgesehen — mit der stärkeren Ermüdung im Dreinächteversuch zusammenhängen dürfte.

Die Vp. der Serien 2—5, die sich zu Beginn des Laufes ausgeruht gefühlt hatten, zeigen eine erheblich bessere Reaktion: Mittelwert

Tabelle 2.

Die Einwirkung von Benzodrin und Pervitin auf die Leistung im Geländelauf über 3 km nach Ermüdungsübungen während dreier Nächte und der Zwischentage. In der Tabelle sind auch die Ergebnisse derjenigen angegeben, die sich bei dem zweiten Lauf ausgeruht gefühlt hatten.

Versuchsserie	1.	2.	3.	4.	5.	6.	2—5
Tabletten 3. Tag 4. Tag.	— Leertabl.	— 20 mg Benz.	— 30 mg Benz.	— 18 mg Perv.	20 mg Benz. 20 mg Benz.	20 mg Benz. Leertabl.	Subjektiv ausgeruht bei dem Lauf
1. Lauf Mittelwert, Min. ....	21.06	21.00	20.18	20.42	21.04	21.30	
2. Lauf Abnahme — bessere Leistung:							
Anzahl d. Sek. ....	—1200	—10850	—11965	—6930	—5880	—3500	—11550.
» » Vp. ....	20	49	52	33	35	14	49
Unverändert (—30—+30):							
Anzahl d. Vp. ....	15	23	19	15	21	16	54
Zunahme — Verschlechterung:							
Anzahl d. Sek. ....	+29540	+11970	+8400	+9170	+15540	+19200	+280
Anzahl d. Vp. ....	77	46	34	41	55	83	2
Ergebnis:							
Gesamtveränderung in							
Sek. ....	+25340	+1120	—3655	+2240	+9660	+15700	—11270
Anzahl d. Vp. ....	113	118	105	92	111	113	105
Medium, Sek. ....	+224±32	+10±26	—34±27	+24±29	+87±24	+139±26	—110±21



— 110 Sek.; der Unterschied zwischen dem Mittelwert dieser Vp. und dem der Kontrollserie (Ser. 1) beträgt also  $-110 - +224 = 334$  Sek. Somit eine erhebliche Steigerung der Leistungsfähigkeit: Mittelwerte der so »ausgeruhten« Vp. im zweiten Lauf etwa 20 Min., in der Kontrollserie fast 25 Min; die ersteren brauchten also eine etwa 20 % kürzere Zeit.

Die bisher vorliegenden einschlägigen Untersuchungen haben zwar nicht mit so hochgradig ermüdeten Vp. gearbeitet, doch zeigen sie eindeutig die Kraft der fraglichen Stoffe, vorhandene Müdigkeitserscheinungen zu beheben oder ihr Auftreten bei anstrengender Tätigkeit zu verzögern. Die Wirkung hat man so ausgedrückt, dass die Müdigkeitsgrenze näher an die absolute Erschöpfungsgrenze gerückt wird.

Lehmann, Straub und Szakáll, 1938—39, sowie Szakáll, 1939, fanden, dass Pervitin bei Versuchen am Fahrradergometer die Ermüdungserscheinungen hinausschiebt, und zwar sowohl zeitlich bei fortlaufender gleichbleibender Anspannung als in bezug auf die Höhe der Belastung bei allmählich ansteigender Belastung. — Heyrodt und Weissenstein, 1940, sahen bei einer geübten Langstreckenläuferin auf der Tretbahn nach Verabfolgung von Pervitin erhöhte Ausdauer.

Die Erscheinungen, die von den genannten Autoren als indirekte Pervitinwirkung in Form von zu weit getriebener Ermüdung gedeutet werden, lassen sich mit grösserer Wahrscheinlichkeit als medikamentelle Intoleranzsymptome nach der grossen Dosis von 30 mg Pervitin erklären.

Kürzlich hat Pellmont, 1942, die Resultate vergleichender Untersuchungen über die Wirkungen von Coramin, Coffein und Pervitin auf psychische und physische Leistung des ermüdeten und nicht ermüdeten Menschen vorgelegt. An der sog. »grossen Versuchsreihe« nahmen 10 wohltrainierte Sportler teil, die durch ein offenbar kurzdauerndes hartes, vielseitiges Mehrkampftraining ermüdet wurden.  $\frac{1}{2}$  Stunde vor Beendigung des Trainings wurde 6 mg Pervitin verabfolgt, worauf 1 Stunde lang Proben angestellt wurden, u. a. Kraftproben: Dynamometer-, Hantel- und Expanderversuch. Das Pervitin erhöhte die durch die Ermüdung geschwächte Leistungsfähigkeit (in Versuchen mit Leertabl. ermittelt) auf denselben Stand wie beim nicht ermüdeten Menschen.

Wenn auch in den vorliegenden Versuchen die Leistung in gewissen Fällen die im ersten Lauf gezeigte zu übersteigen scheint, muss doch mit der Möglichkeit gerechnet werden, dass zufällig hereinspielende Faktoren (Witterung, Beschaffenheit und Kenntnis der Bahn) die Schwierigkeit der Probe vermindert und so den Anschein gesteigerter Leistung erweckt haben. Doch liegt wahrscheinlich trotz der Ermüdung absolute eine Leistungssteigerung vor.

Aus Tabelle 2 ist ferner zu ersehen, dass etwa 24 Stunden vorher verabreichtes 20 mg Benzedrin (Ser. 6) hinsichtlich des Mittelwertes noch wirksam ist. Der Unterschied zwischen Ser. 1 und Ser. 6 ist zwar nicht statistisch gesichert, aber doch wahrscheinlich. Es ist dabei in Betracht zu ziehen, dass die Vp. in Ser. 6 sich am vorletzten Tage infolge der anregenden Wirkung des Benzedrins zweifellos bedeutend mehr angestrengt und die sich bietenden kurzen Augenblicke zum Schlafen schlechter ausgenutzt haben als Ser. 1—4.

Ser. 5 bekam je 20 mg Benzedrin am 3. und 4. Morgen. Die zweite Dosis Benzedrin hat zwar eine starke Wirkung, die aber doch nicht so gross ist wie die Wirkung der gleich hohen einmaligen Dosis in Ser. 2. Der Unterschied zwischen Ser. 1—5 und 5—6 ist nicht sicher signifikant, jedoch höchst wahrscheinlich.

Dies dürfte damit zu erklären sein, dass Ser. 5 ebenso wie Ser. 6 bei den Übungen des Vortages stärker ermüdet war als die übrigen. Deshalb reagiert Ser. 5 nicht so gut auf die wiederholte Dosis. Dies mag merkwürdig erscheinen, da der Wert in Ser. 6 für eine fortwährende Benzedrinwirkung spricht. Man erwartet deshalb einen stärkeren Effekt der zweiten Dosis von 20 mg Benzedrin in Ser. 5. Vielleicht war eine noch grössere Dosis nötig, um denselben Effekt in Ser. 5 wie in Ser. 2 zu geben. Es ist aber auch möglich, dass die Kraftreserven dieser Vp. so erschöpft waren, dass nicht einmal mehr die Bedingungen für eine Benzedrinwirkung von gleicher Stärke wie in Ser. 2 gegeben sind. Von diesem Gesichtspunkt aus braucht also kein Widerspruch darin zu liegen, dass in Ser. 6 eine gewisse noch anhaltende Benzedrinwirkung festzustellen ist, gleichzeitig aber in Ser. 5 die Benzedrinwirkung weniger stark hervortritt als in Ser. 2. Es wäre sicherlich unrichtig, aus den hier erzielten Resultaten den Schluss zu ziehen, die Wirkung wiederholter Benzedrindosen sei durchweg geringer. Im übrigen sei auf die frühere Diskussion (Alwall, 1943) verwiesen.

### *Zusammenfassung von Kap. I.*

Benzedrin und Pervitin in einmaliger Dosis am Morgen des letzten Tages steigert die Leistung im Geländelauf von Vp., die zwei oder drei Nächte hintereinander und an den dazwischenliegenden Tagen durch Schlaflosigkeit und körperliche Anstrengungen ermüdet sind. Diese Wirkung ist markanter bei den Vp., die sich nach Ein-

nahme der Stoffe ausgeruht gefühlt oder unangenehme Nebenwirkungen verspürt haben, d. h. bei empfänglicheren Personen.

Die Ergebnisse stehen im Einklang mit einschlägigen Angaben in der Literatur, die jedoch nicht aus Versuchen mit ebenso stark ermüdeten Vp. herrühren.

Die Wirkung von 20 mg Benzedrin, am vorletzten Tage des Dreinächteversuchs verabfolgt, dauert wahrscheinlich mindestens 24 Stunden an.

## Kap. II. Studien über die Wirkung von Benzedrin und Pervitin auf die psychische Leistungsfähigkeit.

### Die Bedeutung des Ermüdungsgrades für die Wirkung-Dosierung des Benzedrins.

Dieser Abschnitt umfasst Versuche mit A. Bourdon-Tests und B. Rechtentests sowie C. Zusammenfassung.

Der erste psychotechnische Test wurde bei der Rückkehr ins Quartier nach Abschluss der Ermüdungsübungen vorgenommen. Anschliessend wurden die Tabletten ausgeleilt, und zwar Leertabletten für die Kontrollserie, Benzedrin- oder Pervitintabletten für die übrigen. 1 ½—2 Stunden später wurde der psychotechnische Test mit neuem Text bzw. neuen Rechenaufgaben wiederholt.

Sämtliche Teilnehmer führten den Test zugleich aus, und zwar bekam auch jede Vp. bei beiden Tests den gleichen Platz im Prüfungsraum, damit Unterschiede in der Beleuchtung vermieden würden. Der Versuchsleiter gab den Zeitpunkt für Beginn und Schluss der Prüfung. Um Gleichzeitigkeit und Kontrolle zu gewährleisten, waren bei den grossen Versuchsreihen — bei einer Prüfung über 700 Vp. — besondere organisatorische Vorkehrungen getroffen worden.

Durch einen orientierenden Versuch waren die Vp. im voraus mit der Untersuchungstechnik vertraut gemacht worden.

#### A. Bourdon-Testversuche.

Die Tabellen 3 und 4 verzeichnen die Ergebnisse der Bourdon-testversuche, die nach den Dreinächteübungen ausgeführt worden sind.

Der erste Testversuch wurde gegen 4.45 Uhr früh, der zweite gegen 8 Uhr morgens, etwa 1 ½ Stunden nach Ausgabe der Tabletten durchge-

**Tabelle 3.**  
Einwirkung von Benzodrin und Pervitin auf die Anzahl gelesener Buchstaben und den Fehlerprozent im Bourdon-Test nach Ernüdungsübungen während dreier Nächte und der Zwischentage. Betr. Dosierung usw. siehe Tabelle 1 und den Text.

Versuchsserie	1.	2.	3.	4.	5.	6.	2.—5.
<i>Probe 1</i>							
Mittelwerte, Anzahl d. Buchstaben .....	92.2	91.4	91.7	93.4	90.0	91.3	Subj. Gefühl:
Fehlerprozent .....	13.0	12.1	10.8	10.5	11.2	11.9	»ausgeruht«
<i>Änderung d. Anz. Buchst. von Probe 1 bis 2</i>							
a) Prozent .....	+21.6	+31.6	+33.3	+32.5	+32.1	+28.2	
b) absolute Zahlen:							
Zunahme: Anzahl d. Buchstaben .....	+1809	+2088	+2286	+2160	+1665	+1845	+3582
Anzahl d. Versuchspersonen ..	78	80	87	73	63	72	129
Unverändert (+4—4):							
Anzahl d. Versuchspersonen ..	15	10	9	11	9	16	12
Abnahme: Anzahl d. Buchstaben .....	—189	—171	—270	—126	—126	—216	—189
Anzahl d. Versuchspersonen ..	9	12	11	9	8	11	13
<i>Ergebnis: Gesamtänderung d. Anz. Buchst. ....</i>	+1620	+1917	+2016	+2034	+1539	+1629	+3393
Anzahl d. Versuchspersonen ..	102	102	107	93	80	99	154
Medium .....	+15.9±1.9	+18.8±1.9	+19.0±2.0	+21.9±2.2	+19.2±2.0	+16.5±2.1	+22.0±2.2

Tabelle 4.

Einwirkung von Benzedrin und Pervitin auf die Anzahl der im Bourdon-Test nach Ermüdungsübungen während dreier Tage und der Zwischentage erzielten Punkte. Betr. Dosierung usw. siehe Tabelle 1 und den Text.

Versuchsserie	1.	2.	3.	4.	5.	6.	2.—5.
<i>Probe 1</i>							
Mittelwert, Punktzahl ....	68.3	69.3	72.0	73.9	69.9	69.5	Subj. Gefühl: „ausgeruht“
Änderung von Probe 1 bis 2							
a) Prozent .....	+21.6	+31.6	+33.3	+32.5	+32.1	+28.2	
b) absolute Zahlen:							
Zunahme: Anzahl d. Punkte	+1809	+2349	+2881	+2358	+1890	+2223	+4401
Anzahl d. Versuchspersonen ..	78	82	84	75	63	76	137
Unverändert (+1—4):							
Anzahl d. Versuchspersonen ..	8	14	12	7	10	6	8
Abnahme: Anzahl d. Punkte	—306	—117	—216	—126	—99	—297	—108
Anzahl d. Versuchspersonen ..	16	6	24	11	7	17	9
<i>Ergebnis: Gesamtänderung</i>							
der Punktzahl ....	+1503	+2232	+2565	+2232	+1791	+1944	+4293
Anzahl d. Versuchspersonen ....	102	102	107	93	80	99	154
Medium .....	+14.7 ± 2.1	+21.9 ± 2.1	+21.0 ± 2.1	+21.0 ± 2.1	+22.3 ± 2.5	+19.6 ± 2.3	+28.0 ± 2.3

führt. Betreffs der Verteilung und Dosierung der Tabletten siehe Tabelle 2 sowie Alwall, 1943. Während einer Zeit von 3 Minuten hatten die Vp. aus einem vorgelegten Text zwei Buchstaben zu streichen. Bewertet wurden die Lesegeschwindigkeit (Anzahl gelesener Buchstaben) und die Genauigkeit — die Punktzahl errechnet sich aus der Anzahl richtig gestrichener Buchstaben abzüglich der übersehenen und falsch durchgestrichenen.

Der Test liefert also einen Gradmesser für die Fähigkeit zu kurzdauernder gespannter Aufmerksamkeit.

Die Mittelwerte sind praktisch im ersten Versuch sämtlicher Serien die gleichen, ebenso die Fehler-%-Werte. Im zweiten Versuch steigt die Anzahl der Möglichen in Ser. 2—4 mehr als in der Kontrollserie, Ser. 1.

Die in Ser. 5 und 6 gewonnenen Ergebnisse werden in einer anderen Arbeit besprochen (Alwall, 1943).

Tabelle 3 zeigt die Verteilung der individuellen Unterschiede zwischen der Leistung im ersten und zweiten Testversuch. Die Unterschiede zwischen Ser. 1 einerseits und Ser. 2—4 andererseits können zwar nicht als statistisch gesichert gelten, doch scheint es ziemlich klar, dass Benzodrin und Pervitin die Lesegeschwindigkeit steigern.

Die Tabletten verursachen eine zwar statistisch nicht restlos gesicherte, aber doch ziemlich klare Verbesserung der Genauigkeit, ausgedrückt in der Anzahl der erzielten Punkte, wie aus Tabelle 4 hervorgeht. Am deutlichsten ist diese Wirkung bei den Vp. der Ser. 2—5 zu vermerken, die sich beim zweiten Testversuch ausgeruht fühlten. *Wir finden somit, dass Benzodrin und Pervitin bei diesen ermüdeten Versuchspersonen vermutlich die Lesegeschwindigkeit und mit grösster Wahrscheinlichkeit die Genauigkeit im Bourdonschen Testversuch steigern.*

Die Sicherheit der Resultate leidet in gewissem Grade unter der grossen Leistungssteigerung, die in sämtlichen Serien zwischen dem ersten und dem zweiten Versuch eingetreten ist. Folgende Erklärungsmöglichkeiten für diese Steigerung lassen sich in Betracht ziehen: 1) bessere Übung beim zweiten Versuch? (doch dürfte sich dieses Moment weniger stark geltend machen, da vor dem ersten Versuch ja schon ein Instruktionsversuch gemacht worden war und da weiter der Test in nur 3 Minuten durchgeführt wurde); 2) leichtere Buchstaben in Versuch 2? (im ersten Versuch wurden n und l gestrichen, im zweiten e und k); 3) die Anzahl der beiden zu streichenden Buchstaben war im zweiten Versuch grösser? (das war indessen nicht der Fall: a) in den ersten fünf Zeilen im ersten bzw. zweiten Versuch waren 33 bzw. 32 Buchstaben zu streichen, b) in den ersten 10

Zeilen 61 bzw. 61, in 15 Zeilen 95 bzw. 88 und c) in 20 Zeilen 124 bzw. 121); 4) die zweistündige relative Ruhe in Verbindung mit Mahlzeit zwischen den beiden Proben genügte für eine erhebliche Erholung?; 5) der Tagesrhythmus, welche Möglichkeit im folgenden näher erörtert wird.

Im Zusammenhang mit den Rechentests der ermüdeten Vp. wurden Bourdon-Tests ausgeführt, deren Ergebnisse nicht von den hier genannten abweichen. Sie werden im folgenden mitgeteilt werden.

Die im Schrifttum vorliegenden Angaben über die Einwirkung von Benzedrin oder Pervitin auf die Leistung im Bourdon-Test betreffen nicht ermüdete Personen.

Lehoczky, 1938, schreibt kurz, ohne Material vorzulegen: »Mit objektiven Testversuchen ist eine Zunahme der Konzentrationsfähigkeit festzustellen, beim Bourdon-Testversuch ist am häufigsten die Abnahme der Zeitdauer sowie der Fehler zu konstatieren.«

Csirády und Dirner, 1939, fanden steigende Bourdon-Fehler-%-Werte nach 20 mg Benzedrin bei 5 nicht ermüdeten Versuchspersonen, die an verschiedenen Tagen einer Reihe von Tests ohne vorherige Aufnahme von Medikamenten bzw. nach Einnehmen von solchen, u. a. Pervitin, unterzogen worden waren. »Die Prüflinge hatten 3 der Abbildungen des Bourdonschen Tests, die zugleich 10 Sek. lang exponiert worden waren, in den ersten 10 Zeilen des Textes vor dem Wörterlernen und in anderen 10 Zeilen 3 andere Abbildungen am Ende des Versuches zu durchstreichen.« In den Kontrollversuchen am ersten und letzten Tage ergaben sich 1.25 (Grenzen 0.25 — 4.0) bzw. 2.95 % Fehler (1.0 — 9.25), Werte, die in den erlaubten Grenzen bleiben. Nach Pervitin 9.25 % Fehler (Grenzen 5.75 — 11.75 %).

Wollstein, 1939, sah keine sichere objektive Wirkung von 15 mg Benzedrin auf die Leistungen einer grösseren Anzahl ausgeruhter Versuchspersonen in einem Bourdon-Test von 10 Minuten Dauer (Streichen von 4 Buchstaben).

Lemmel und Hartwig, 1940, wandten folgendes Verfahren an: » $\frac{1}{2}$ —2 Stunden nach Einnahme des Präparates wurde zunächst mit dem Abstreichtest von 5 Min. Dauer begonnen. Unmittelbar darauf wurde 3mal je 1 Min. gerechnet. Darauf wieder 5 Min. Abstreichtest und 3mal je 1 Min. Rechentest. Abstreichtest und Rechentest wurden in diesem Wechsel jeweils 7mal ohne grössere Pausen im Verlaufe von etwa 70 Min. hintereinander wiederholt. Gewertet wurde bei jedem Versuch stets nur die Summe der 7 Abstreichtests von je 5 Min. Dauer und die Summe der 7mal Rechentests von je 1 Min. Dauer.« — 5 Versuchspersonen, die an verschiedenen Tagen mit Kontrolltabletten, Benzedrin oder Pervitin geprüft wurden. Die verabfolgten P- und B-Dosen sind nicht angegeben.

Beim Bourdon-Test, wobei 3 Buchstaben zugleich abgestrichen wurden, steigerten die verabfolgten Stoffe das Arbeitstempo mit 4.3—6.1 % Zunahme der abgestrichenen Buchstaben im Vergleich zum Leerversuch.

Die Fehlerzahl nahm trotz des beschleunigten Tempos ab. Benzedrin oder Pervitin haben also das Arbeitstempo gesteigert, ohne dass darunter die Genauigkeit, oder die Konzentrationsfähigkeit, leidet, sondern sich eher etwas bessert.»

Eine direkte Vergleichung der einander widersprechenden Angaben des Schrifttums und der oben angeführten Ergebnisse ist wegen der unterschiedlichen Versuchsbedingungen und der in der Regel kleinen Versuchsreihen nicht möglich. Wie im folgenden eingehender erörtert wird, spielen nicht nur der Grad der Müdigkeit, sondern zweifellos auch die Dosierung und die individuelle Empfindlichkeit gegen die eingenommene Dosis eine entscheidende Rolle für das Ergebnis.

### B. Rechentestversuche.

(Nebst einigen Bemerkungen zur Bedeutung der Müdigkeit für die Wirkung-Dosierung des Benzedrins.)

Nach Ermüdung waren 15 Min. lang ohne Unterbrechung einfachere Rechenaufgaben im Kopf zu lösen. In den vorgelegten Aufgaben sollten gewisse ausgelassene Zahlen eingesetzt werden. Die 140 Aufgaben umfassten alle vier Rechnungsarten. Die Aufgaben waren so ausgearbeitet und zusammengestellt, dass keine allzu leichten und allzu schweren Kombinationen vorkamen. Bei der Wertung wurde teils die Schnelligkeit (die Anzahl gelöster Aufgaben) berücksichtigt, teils die Sicherheit (die Fehlerprozentzahl). — Eine kleinere Anzahl nicht ermüdeter Vp. musste teils 15 Min. lang dieselben Aufgaben lösen, die den Ermüdeten vorgelegt worden waren, teils in 10 Min. bedeutend schwerere Aufgaben. Nach dem ersten Versuch wurden Tabletten ausgegeben, und nach etwa 1 ½ Stunden wurde der Rechentest mit neuen, doch gleichartigen Aufgaben wiederholt.

In der Literatur setzt man die Sicherheit der Leistung beim Rechentest im wesentlichen auf das Konto der Merkfähigkeit. Die Schnelligkeit wird als eine Folge des Konzentrationsvermögens angesehen: kann man sich nicht konzentrieren, so verliert man den Zusammenhang und muss noch einmal von vorn anfangen.

Bevor ich über die Einwirkung von Benzedrin auf das Rechenvermögen ermüdeter Vp. eingehe, gebe ich — im Anschluss an Literaturreferate — die Resultate von eigenen Versuchen über die Einwirkung von Benzedrin auf das Rechenvermögen nicht ermüdeter Vp. an.



# 1. Die Wirkung von 20 mg Benzedrin auf das Rechenvermögen nicht ermüdeter Versuchspersonen.

Die in der Literatur begegnenden Angaben über die Einwirkung von Pervitin und Benzedrin auf das Rechenvermögen nicht ermüdeter Vp. sind widerspruchsvoll.

Im Zusammenhang mit ihren in diesem Kapitel schon erwähnten Untersuchungen über die Einwirkung von 20 mg Benzedrin auf die Resultate in Bourdon-Tests an 5 Vp. fanden Csirády und Dirner, 1939, auch eine Abnahme des Rechenvermögens in einer Reihe einfacherer Aufgaben. An den beiden Kontrolltagen wurden von 36 möglichen Aufgaben durchschnittlich 31.6—30.4 Aufgaben gelöst; nach Einnahme von Benzedrin nur 23.4.

Die Streuung der Ergebnisse in diesen kleinen Versuchsreihen ist jedoch gross. Die Grenzen der Anzahl gelöster Aufgaben waren an den beiden Kontrolltagen 29—35 bzw. 25—35; in der B-Reihe 9—31. Die Ergebnisse sind in Anbetracht dieser Streuung weniger sicher.

Lemmel und Hartwig: Zunahme der addierten Zahlen um 4.0—4.3 % nach Einnahme einer nicht angegebenen Menge Benzedrin oder Pervitin. Die Zahl der Fehler auf je 100 addierte Zahlen fiel von 3.2 im Leerversuch auf 2.8 bzw. 2.7.

Lehoczy, 1938: »Bei dem Additions-Testversuch nach Kräpelin erhielten wir bei einem Teil der Fälle ein besseres Resultat, bei den übrigen zeigte sich nur eine geringe oder unbedeutende Änderung.«

Versuchspersonen waren nicht-ermüdete Studenten der Medizin.

Um 8 Uhr morgens mussten diese erst im Laufe von 15 Min. einen Rechenversuch ausführen, der dieselben Aufgaben enthielt wie die in den späteren Versuchen mit ermüdeten »ungebildeten« Soldaten verwendeten. Im folgenden nenne ich diese Aufgaben den »leichten Rechentest«. Nach einer Pause von 10 Min. folgte der »schwere Rechentest«, der 10 Min. dauerte. Im Anschluss daran erhielt die eine Hälfte der Vp. Leertabletten und die andere Hälfte 20 mg Benzedrin. Nach etwa 2 ½ Stdn. folgte ein erneuter »leichter Rechentest« während 15 Min. und nach 10 Min. Pause ein »schwerer Rechentest« während 10 Min.

Die Aufgabe war in beiden Tests dieselbe: nach Kopfrechnung ausgelassene Zahlen einzusetzen. Der Schwierigkeitsgrad der Versuche erhellt aus der mittleren Anzahl der in 15 Min. (leichte) bzw. 10 Min. (schwere) gelösten Aufgaben im ersten Versuch: etwa 80 bzw. 18. Folgende Aufgaben sind den verschiedenen Versuchen entnommen. (Vorausgesetzt ist, dass die Summe der Zahlen links von einem Gleichheitszeichen gleich der ersten Ziffer rechts vom Gleichheitszeichen ist.) Leichte:  $( ) + 19 = 30 + ( )$  —  $8 = 23$ ; 49:  $( ) = ( ) + 7 = 14$ ;  $( ) \times 2 - 3 = 19 - ( ) = 13$ . Schwere:  $7 \times 15 = ( ) + 27 + ( ) = 264$ ; 36:  $( ) = 4 \times ( ) - 63 + 81 = 162$ ;  $( ) - 27 = ( ) - 49$ ;  $7 = 52$ .

Tabelle 5.

Einwirkung von 20 mg Benzedrin auf das Rechenvermögen ausgeruhter Versuchspersonen.

Versuchsserie	Leichte Rechenaufgaben (15 Min., 15 Vp.)		Schwere Rechenaufgaben (10 Min., 17 Vp.)	
	Leertabl.	20 mg Benz.	Leertabl.	20 mg Benz.
1. Probe				
Gelöste Aufgaben, Mittelwert ..	81.1	78.2	18.6	17.6
Fehlerprozent .....	5.8	6.1	18.0	15.8
Änderung von 1.—2. Probe				
Anzahl d. gelösten Aufgaben %	+38	+37	+63	+47
• Fehler % .....	— 9	+39	—39	+95

Das Ergebnis des *leichten Rechentests* (Tabelle 5) lässt sich wie folgt zusammenfassen: In beiden Reihen nimmt die Anzahl der gelösten Aufgaben im zweiten Versuch in gleichem Grade zu. Die Fehleranzahl in der Kontrollserie nimmt etwas ab, nimmt dagegen in der Versuchsserie zu. 20 mg Benzedrin haben also in geringem Grade die Fähigkeit zur Lösung der leichten Aufgaben herabgesetzt.

Im *schweren Rechentest* (Tab. 5) steigt die Arbeitsleistung in beiden Serien an, aber mehr in der Kontrollserie. Die Fehleranzahl nimmt in der Benzedrinserie stark zu, während sie in der Kontrollserie abnimmt (—39 bzw. + 95 %). 20 mg Benzedrin haben eine ungünstige Einwirkung besonders auf die Sicherheit bei Aufgaben dieses Schwierigkeitsgrades.

Die verschieden lange Versuchsdauer dürfte auf die Ergebnisse ohne Einfluss sein. Der schwere Rechentest wurde in kürzerer Zeit durchgeführt, damit sich nicht die Ermüdung zu sehr geltend machen sollte. Man könnte nämlich vermuten, dass bei längerer Versuchsdauer sich eine müdigkeitsbekämpfende Wirkung des Benzedrins geltend gemacht haben könnte, wodurch der ungünstige Effekt hätte ausgeglichen werden können.

*Es hat sich somit gezeigt, dass eine Dosis von 20 mg Benzedrin das Rechenvermögen ausgeruhter Vp. um so schwerer stört, je schwerer die vorgelegte Aufgabe ist, d. h. je höhere Anforderungen an die Konzentrationsfähigkeit gestellt werden.*

Hier haben wir vielleicht die Erklärung für die einander widersprechenden Angaben der Literatur. Bestimmend für das Ergebnis dürften im Einzelfall sein 1) die Grösse der Dosis, 2) die früher

(Alwall, 1943) hervorgehobene, von der zufälligen Disposition (Ermüdung usw. bestimmte Reaktion der betreffenden Person auf eine gewisse Dosis, 3) die Art der Arbeitsaufgabe; je schärfere Konzentration erforderlich ist, um so nachteiliger wirkt sich eine Überdosierung aus. Als Überdosierung wird in diesem Falle eine Dosis betrachtet, die über der in einer bestimmten Situation für die betreffende Person optimalen Gabe liegt, 4) Die individuelle Reaktion auf diese Substanzen.

## 2. Die Wirkung von 20 mg Benzedrin auf das Rechenvermögen ermüdeter Versuchspersonen.

Um die Bedeutung des Grades der Ermüdung für die Benzedrinwirkung zu untersuchen, wurde die Einwirkung einer gleichbleibenden Benzedrindosis auf ermüdete Vp. in verschiedenen Versuchsreihen miteinander verglichen; in der einen Serie wurden die Versuche in den frühen Morgenstunden, bevor es dämmerte, wo die Müdigkeit nach dem normalen Tagesrhythmus am stärksten ist, ausgeführt. In der zweiten Serie wurden die Versuche am Vormittag des gleichen Tages durchgeführt, wo die Müdigkeit, und Schläfrigkeit spontan nachgelassen hat.

Etwa 200 Vp. im Alter von ungefähr 21 Jahren musste in 2 aufeinander folgenden Nächten (Anfang Mai) schwerere körperliche Arbeit tun. An dem dazwischenliegenden Tage verschiedene Übungen ohne Möglichkeit zu schlafen. 1) Die eine Hälfte der Mannschaft marschierte in der letzten Nacht um 24 Uhr ins Quartier zurück. Nach Durchführung eines Bourdon-Tests von 3 Minuten Dauer, gefolgt von 10 Min. Ruhe und einem 15 Min. dauernden Rechentest erhielt die eine Hälfte der Männer zusammen mit Weissbrot und Kaffee Leertabletten, die übrigen 20 mg Benzedrin. Nach etwa 1 ½ stündigen weiteren Übungen wurden gleichartige Tests, doch mit neuen Aufgaben, durchgeführt. Die Versuche waren bis zur Morgendämmerung beendet. 2) Die zweite Hälfte der Mannschaft musste ohne Unterbrechung bis 8 Uhr morgens weiterarbeiten, worauf sie ebenfalls die Tests ausführen musste und Tabletten erhielt. Die im Bourdon- wie im Rechentest vorgelegten Aufgaben waren für beide Gruppen die gleichen, und zwar die in den oben erwähnten Versuchen (die Bourdontests bzw. die leichten Rechenaufgaben) angewandten.

Die Ergebnisse sind aus Tabelle 6 zu entnehmen. Die Anzahl der gelösten Rechenaufgaben nahm von der ersten zur zweiten Probe ein wenig zu: 2—9 %. Die Anzahl der Fehler erhöhte sich in der Kontrollserie des Nachtversuchs um 47 %, in der Benzedrinserie um nur 27 %; das Benzedrin hatte also eine Leistungsbesserung bewirkt.

Tabelle 6.

Die Einwirkung von 20 mg Benzodrin auf das Rechenvermögen im Nacht- bzw. Tagversuch.

Versuchsserie	Nachtversuch (46 Vp.)		Tagesversuch (45 Vp.)	
	Leertabl.	20 mg Benz.	Leertabl.	20 mg Benz.
<i>1. Probe</i>				
Gelöste Aufgaben, Mittelwert ..	43.7	47.4	44.2	45.0
Fehlerprozent .....	8.0	7.2	9.6	8.7
<i>Änderung von 1.—2. Probe</i>				
Anzahl d. gelösten Aufgaben %	+ 2	+ 8	+ 9	+ 9
„ „ Fehler % .....	+47	+27	+13	+32

Im Tagesversuch betrug die Steigerung der Fehleranzahl 13 bzw. 32 %; hier hatte also das Benzodrin das Rechenvermögen verschlechtert. Diese Verschlechterung erreicht nicht die gleiche Grössenordnung wie die in den Versuchen mit nicht-ermüdeten Vp. in Tabelle 5.

Trotz der verschiedenen Anzahl der Vp. in den verschiedenen Serien, trotz der durch die grosse Steigerung der Arbeitsleistung in der zweiten Probe der Studenten und trotz des verschiedenen intellektuellen Trainings usw. der Studenten und der Soldaten scheinen doch die Resultate einen Beitrag zur Frage der Bedeutung des Ermüdungsgrades für die Wirkung-Dosierung des Benzodrins zu erlauben. Es seien folgende Kommentare gemacht.

1) Die leichten Rechenaufgaben in Tabelle 5 und die Aufgaben in Tabelle 6 sind die gleichen. Die Studenten schaffen fast doppelt so viele Aufgaben und die Fehler-%-Zahl ist etwas kleiner. Für die gewöhnlichen Rekruten (Tab. 6) sind teils die Aufgaben relativ schwerer, teils kommt die Ermüdung hinzu. Die relative Schwierigkeit für die Soldaten dürfte zwischen derjenigen der leichten und der schweren Rechenaufgaben für die Studenten liegen. Man dürfte deshalb bei etwaiger Überdosierung unter den Soldaten einen relativ grossen negativen Ausschlag erwarten können.

2) In der Kontrollserie des Nachtversuchs nimmt die Fehlerzahl bedeutend mehr zu als in der des Tagesversuchs. Dies dürfte darauf beruhen, dass im Nachtversuch die zweite Probe zur Zeit der stärksten Müdigkeit, nämlich im Morgengrauen, vorgenommen wird. Die Vp. des Tagesversuchs dagegen führen ihre zweite Probe später am Tage aus, wo die Müdigkeit spontan abnimmt.

3) Die relativ bessere Leistung nach Einnahmen von Benzodrin während der Nacht dürfte darauf zurückzuführen sein, dass die Müdigkeit nachts

stärker ist, so dass eine grössere Anzahl von Vp. günstig auf die darge-reichte Dosis reagiert hat. 4) Dieselbe Dosis, die die Ergebnisse im Nacht-versuch verbessert, verschlechtert die Ergebnisse des Tagesversuchs, trotzdem die betreffenden Vp. 8 Stunden länger ohne Schlaf und den Anstrengungen ausgesetzt waren.

*Die Erklärung dürfte sein, dass 20 mg Benzedrin in diesen Ver-suchen den stark Ermüdeten hilft (der Ermüdungsgrad war am gröss-ten im Nachtversuch), dass die Dosis aber in mehreren Fällen für die weniger Ermüdeten (im Tagesversuch) zu gross ist, und dass die Dosis besonders für die gar nicht ermüdeten Studenten in grösserem Umfang Überdosierung bedeutet und Gedankenflucht sowie vermin-derte Konzentrationsfähigkeit verursacht.*

Ganz analog bewirkt der Tagesrhythmus, dass z.B. dieselbe Dosis Luminal am Tag als Sedativum, in der Nacht als Hypnoticum wirken kann.

Ungünstige Wirkung zu Beginn bei den weniger Ermüdeten schliesst natürlich einen späteren günstigen Effekt nicht aus, wenn der Versuch so in die Länge gezogen wird, dass sich die Müdigkeit normalerweise geltend zu machen und das Rechenvermögen zu schwächen beginnt. Auf diese Weise kann es natürlich doch vor-teilhaft sein, in einer bestimmten Situation z. B. 20 mg Benzedrin zu verabfolgen, wenn sich die Arbeitsleistung über längere Zeit hin-ziehen soll. Richtiger dürfte es aber oft sein, in einem solchen Falle anfangs überhaupt kein Benzedrin oder Pervitin zu verabfolgen, oder doch nur in einer so kleinen Dosis, dass keine Störungen auf-treten. Später sind bei Bedarf sukzessiv kleinere Mengen zu ver-abreichen, was möglich ist, da sich die Wirkung bereits nach  $\frac{1}{4}$ — $\frac{1}{2}$  Stunde zeigt.

Im Schrifttum liegen einige Mitteilungen über die Einwirkung von Benzedrin oder Pervitin auf das Rechenvermögen ermüdeter Personen vor. Der Grad der Ermüdung ist jedoch nicht derselbe wie in den hier referierten Versuchen oder die Angaben sind zu knapp gehalten, um kritische Vergleiche zu ermöglichen.

Ohne Einzelheiten anzuführen, schreibt Ranke, 1939, in einem kurzen Autoreferat betr. Leistungssteigerung durch ärztliche Massnahmen: »Der Einfluss des Ephedrinabkömmlings Pervitin wurde an 90 Versuchsperso-nen in Nachtversuchen untersucht und dabei an Schreib- und Rechenpro-ben festgestellt: Die Arbeitsmenge und die Vermeidung von Fehlleistun-gen bei stumpfsinniger geistiger Arbeit sind im ermüdeten Zustand ohne Pervitin schlechter als mit Pervitin. Kurzdauernde hohe Konzentration und die Merkfähigkeit wird durch Pervitin kaum verändert.»

Graf, 1939, machte Versuche an 2 Versuchspersonen, die mehrere Tage hintereinander vor und nach Anstrengung im Ergometer Rechenaufgaben lösen mussten. Die erste Probe wurde um 8 Uhr morgens durchgeführt, die zweite 2 ½—4 ½ Stunden später. In fast sämtlichen Versuchen war mit oder ohne Pervitin im zweiten Test eine Leistungssteigerung gegenüber dem ersten Test zu verzeichnen. — 9 mg Pervitin nach dem ersten Versuch verursachte nur bei der einen Vp. eine unverkennbare Besserung der Rechenleistungen, während bei der anderen keine sichere Wirkung festzustellen war.

Pellmont, 1942, liess 10 durch körperliche Übungen ermüdete Sportler u. a. rechnen. »Es müssen  $10 \times 10$  ein- bis zweistellige Zahlen addiert werden. — Diese Probe wurde nach der benötigten Zeit und nach der Anzahl der richtigen Lösungen beurteilt.« — 6 mg Pervitin bewirkte eine gewisse Kürzung der benötigten Zeit, hatte aber auf die Richtigkeit keinen sicheren Einfluss.

Im Zusammenhang mit den Rechentests wurden auch, wie schon gesagt, *Bourdon-Tests* durchgeführt.

Nach Einnahme von 20 mg Benzedrin war in diesen Proben sowohl im Nachtversuch als im Tagversuch eine leichte Besserung sowohl der Lesegeschwindigkeit als der Genauigkeit festzustellen: Mittelwerte im Nachtversuch + 11.4 (+ 6.4) Mögliche und + 5.7 (+ 2.6) Punkte in der Benzedrin- bzw. Kontrollserie, im Tagesversuch entsprechend + 16.0 (+ 10.4) und + 14.5 (+ 12.0). — Kein wesentlicher Unterschied zwischen der Lesegeschwindigkeit im Nacht- und Tagesversuch.

### *Zusammenfassung von Kap. II.*

In diesem Abschnitt wurde die Einwirkung untersucht, die 20 mg Benzedrin auf die psychische Leistungsfähigkeit ausübt, und zwar 1) in Bourdon-Testversuchen an ermüdeten Vp. sowie 2) in Rechentests an nichtermüdeten und ermüdeten Vp.

Vp., die in 3 aufeinander folgenden Nächten und den dazwischenliegenden Tagen keine Gelegenheit zum Schlafen gehabt haben, reagieren nach Einnahme von Benzedrin oder Pervitin mit einer Besserung der Lesegeschwindigkeit und -richtigkeit im Bourdon-Test.

Im Schrifttum liegen keine Untersuchungen über die Wirkungen dieser Substanzen bei Ermüdung dieses Grades vor.

Die Rechenleistung nicht ermüdeter Vp. lässt nach Einnahme von 20 mg Benzedrin nach, und zwar bei schweren Aufgaben stärker als bei leichten. Die Bedeutung der Schwere der vorgelegten Aufgabe beim Studium der Benzedrinwirkung im Rechentest scheint bisher in der Literatur nicht beachtet worden zu sein.

Nach Ermüdung während 1  $\frac{1}{2}$ —2 Nächten und des dazwischenliegenden Tages steigern 20 mg Benzedrin die Rechengeschwindigkeit und senken die Fehler-%-Zahl in Versuchen, die beim Morgengrauen durchgeführt werden, während sich in am Vormittag ausgeführten Versuchen, bei denen die Ermüdungsübungen etwa 8 Stunden länger andauert haben, eine ungünstige Wirkung beobachten lässt. Dies dürfte darauf beruhen, dass die Müdigkeit im normalen Tagesrhythmus um die Frühdämmerung herum am grössten ist und während der hellen Tageszeit abnimmt, und zwar auch nach längerer Schlaflosigkeit. Die Störung durch Benzedrin im Tagesversuch ist nicht so ausgesprochen wie in den Versuchen mit nicht ermüdeten Vp.

Die damit aufgezeigte Bedeutung der augenblicklichen Disposition der Vp. für die Reaktion auf eine bestimmte Menge Benzedrin (oder Pervitin) ist bisher nicht beachtet worden. Eine und dieselbe Dosis kann unter verschiedenen Bedingungen das eine Mal günstig, ein anderes Mal ungünstig, ein drittes Mal überhaupt nicht auf die Leistungsfähigkeit (wenigstens die psychische) einwirken. Voraussetzung für einen gewünschten psychischen Effekt ist also, dass ein Ermüdungszustand o. dgl. vorhanden ist, der behoben werden kann. Wenn dies der Fall ist, so dürfte die Dosis so abzuspassen sein, dass die optimale Dosis nicht überschritten wird.

### Kap. III. Studien über die Einwirkung von Benzedrin auf die Treffsicherheit ermüdeten Schützen beim Scheibenschiessen.

Am ersten Tage des Zweinächteversuches (vor Beginn der Ermüdungsübungen) sowie am Vormittag des letzten Tages (nach Beendigung der Übungen und nach dem Einnehmen der Tabletten und der Durchführung der letzten psychotechnischen Probe) wurde nach der Scheibe geschossen, eine Untersuchungsform, an welche die Vp. gewöhnt waren.

Scheibenschiessen auf 200 m Abstand nach der 5ringigen Scheibe. Nach 3 Probeschüssen, die markiert wurden, schossen die Vp. liegend mit aufgestütztem Gewehr innerhalb von 3 Minuten eine Serie von 10 Schuss, so dass die vorgeschriebene Anzahl Schuss ohne Eile abgegeben werden konnte. Die erzielte Punktzahl ist der Gradmesser der Treffsicherheit.

Das individuelle Versuchsergebnis wird durch den Unterschied zwischen den bei der ersten und der zweiten Probe gezeigten Leistungen angegeben.

Die Mittelwerte der Änderung der Punktzahl vom 1. bis 2. Schiessen in den beiden Versuchsreihen sind etwa die gleichen: + 1.9 für die Benzedrinserie und + 2.4 für die Kontrollserie. Ein

Tabelle 7.

Die Einwirkung von 20 mg Benzodrin auf das Schiessergebnis im Zweinächteversuch: Änderung der Punktzahl vom 1. bis 2. Schiessen:

Beim ersten Schiessen erzielte Punktzahl	Benzodrinserie		Kontrollserie	
	Anzahl d. Vp.	Mittelwert	Anzahl d. Vp.	Mittelwert
50—46	10	— 5.9	5	— 4.3
45—41	34	— 6.6	34	— 1.5
40—36	52	— 1.9	51	— 1.0
35—31	43	+ 1.1	43	— 0.6
30—26	26	+ 4.3	40	+ 3.3
25—21	27	+ 2.4	16	+ 9.5
20—16	21	+ 9.6	20	+ 8.1
15—11	12	+16.2	9	+ 8.0
10—6	8	+11.7	8	+12.0
5—0	6	+19.7	3	+19.0
	239	+1.9	230	+2.4

zuverlässiger Vergleich lässt sich indessen auf dieser Basis nicht anstellen. Eine solche Zusammenstellung kann wesentliche Änderungen der Schiessergebnisse solcher Vp. verschleiern, die vermutlich besonders durch die Tabletten beeinflusst werden, nämlich die guten und mittulguten Schützen. Deshalb ist das Material nach den bei der ersten Schiessprobe erzielten Ergebnissen in Gruppen aufgeteilt und bewertet worden, Tabelle 7. Jede Gruppe umfasst 5 Punkte, so dass also 10 Gruppen entstehen, mit der Punktzahl 50—46, 45—41, 40—36 usw.

Bei den Vp., die beim ersten Schiessen hohe Punktzahlen erreicht haben, liegen die Möglichkeiten zu Änderungen nach Einnahme der Tabletten hauptsächlich in negativer Richtung, während es bei denen, die zuerst schlecht geschossen haben, umgekehrt ist.

In der Punktgruppe 50—46 ist das Mittel der Änderung in der Benzodrinserie kleiner, nämlich —5.9 (—4.3 in der Kontrollserie) Punkte. Markanter ist der Unterschied in der folgenden Gruppe, 45—41 Punkte: —6.6 (—1.5). Auch in der Gruppe 46—40 Punkte ist die negative Änderung in der Benzodrinserie etwas grösser.

Tabelle 8 zeigt die Verteilung der Änderungen in den drei besten Gruppen. Es kann nicht ausgeschlossen werden, dass 20 mg Benzodrin die Treffsicherheit der guten Schützen verschlechtern.



Tabelle 8.

Detailuntersuchung der Schiessergebnisse im Zweinächteversuch. Die Streuung der Veränderungen der Punktzahl in den drei besten Gruppen.

Änderung vom 1. bis 2. Schiessen zur Punktzahl	50—46 Punkte		45—44 Punkte		40—36 Punkte	
	B-Ser.	K-Ser.	B-Ser.	K-Ser.	B-Ser.	K-Ser.
+ 8—12	—	—	—	1	4	5
+ 3—7	—	—	3	7	15	14
+ 2—2	4	2	9	12	13	14
— 3—7	2	2	8	10	8	9
— 8—12	1	1	8	3	6	3
—13—17	2	—	2	1	3	3
—18—22	—	—	2	—	1	2
—23—27	1	—	1	—	—	—
—28—32	—	—	1	—	2	1
Zusammen	10	5	34	34	52	51

Leider war es nicht möglich, durch persönliche Umfragen nach den Gründen der verschlechterten Resultate zu forschen, da das Material erst einige Zeit später bearbeitet werden konnte.

Unter den vorliegenden Versuchsbedingungen lässt sich der etwaige Einfluss der Müdigkeit auf die Treffsicherheit beim Schiessen nicht erkennen.

Aus dem Schrifttum seien einige verwandte Untersuchungen genannt, obwohl Versuchsbedingungen und -methodik einen kritischen Vergleich nicht zulassen.

Pellmont, 1942, fand in Schiessversuchen nach 6 mg Pervitin bei 10 Vp. eine Steigerung um 4 % über den Wert der Leertablettenserie (Zehnerscheiben auf 9 m Distanz; Armeekarabiner mit Lienhard-Einsatz; 5 Schüsse in liegender Stellung). Zur Ermüdung hatten die Leute ein hartes, vielseitiges Mehrkampftraining zu bestehen. Das Material ist nicht in Gruppen aufgeteilt worden. Die Versuchsbedingungen waren also derart, dass ein Vergleich mit den hier vorgelegten Untersuchungen nicht angängig ist.

### Zusammenfassung von Kap. III.

Es wurde die Wirkung untersucht, die eine Dosis von 20 mg Benzedrin auf die Treffsicherheit von Schützen ausübt, die in zwei Nächten und an dem dazwischenliegenden Tage durch militärische Übungen ermüdet waren. Es kann nicht ausgeschlossen werden, dass Benzedrin die Treffsicherheit guter Schützen herabgesetzt hat.

## Zusammenfassung.

Die Wirkungen von Benzedrin und Pervitin auf die physische und psychische Leistungsfähigkeit sind in Versuchen an etwa 1400 jungen, gesunden, hochgradig ermüdeten Versuchspersonen, die in bis zu 3-tägigen Übungen ohne Schlaf ermüdet worden waren, studiert worden. Die Ergebnisse sind in den Zusammenfassungen der einzelnen Kapitel vorgelegt:

I. Die Einwirkung von Benzedrin und Pervitin auf die körperliche Leistungsfähigkeit.

II. Die Einwirkung von Benzedrin und Pervitin auf die psychische Leistungsfähigkeit (Bourdontests, Rechenaufgaben). Ein Beitrag zur Frage der Bedeutung des Ermüdungsgrades (und des Tagesrhythmus) für die Wirkung (Dosierung) des Benzedrins.

III. Die Einwirkung von Benzedrin auf die Treffsicherheit ermüdeten Schützen beim Scheibenschiessen.

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Siehe Alwall, N.: Dies Arch. 1943. Vol. CXIV, fasc. I, Seite 6.

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## Serumcholinesterase in disease.<sup>1</sup>

By

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Choline esterase is an enzyme capable of accelerating the hydrolytic cleavage of choline esters, and then especially of acetylcholine as the only ester which occurs physiologically.

The presence of choline esterase was first demonstrated in the musculature of the heart by Loewi and Navratil during their investigations on the vagus action. It has later been found in all tissues of the organism, though the concentration in nerve tissue is considerably higher than in other places, just as one would expect from what is known regarding the physiology of acetylcholine and its significance for the transmission of nervous effects.

Owing to the central position which choline esterase thus occupies in the normal function of the organism, it is natural that clinicians would soon turn their attention towards this enzyme. After Galehr and Plattner in 1928 had shown that normal blood always contains choline esterase, both in the plasma and in the red blood corpuscles, interest was aroused in the question of this esterase in connection with pathological conditions. At first, special attention was given to myasthenia gravis since Walker had introduced a treatment of this disease with physostigmine which is a specific inhibitor of choline esterase; myasthenia gravis was investigated by Stedman and later by Hicks and Mc Kay. More recently, however,

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<sup>1</sup> Aided by a grant from Nordisk Insulinfond.

attention has also been directed towards the conditions in normal subjects and in patients with other diseases.

With regard to the normal values of serum choline esterase, quite extensive investigations have been reported from various sources. A comparison of results is difficult because of the different methods and units employed<sup>1</sup>, but almost all of them clearly indicate that one must expect wide variations from individual to individual.

Thus Ammon and Voss found in 9 normals that the choline esterase varied between 46 and 33 units. Vahlquist found the variation a little larger, between 25.8 and 51.1 units with a mean of 36, and Jellinek and Looney, using Ammon's technique in 20 cases, found a range between 35 and 136 with a mean of 76 units. Considerably less variation was found by Abdon and Uvnäs in 26 males who gave a mean of 1.11 units, with extreme values of 0.93 and 1.29 units.

All authors found that the choline esterase of the individual remained very constant within the same 24 hours, its variations not exceeding the experimental error, and independently of whether the sample was obtained during fasting or after a meal (Ammon and Voss, Hall and Lucas, Mahal). The variations were found to be larger, however, from day to day, and rather pronounced over a longer period of time (Vahlquist).

The normal physiological processes are without influence on the serum choline esterase. Thus Hall and Lucas, on the basis of extensive data, found that it was not affected by work, fatigue or changes of diet. In women no change was found during menstruation or pregnancy. In experiments on animals Mahal demonstrated that lack of sleep, or changes in the temperature of the environment did not affect the esterase value. He found no difference between the value of arterial and venous blood. At fasting up to 150 hours he found no changes beyond a fall which, however, did not exceed the experimental error; feeding with glucose caused no change of esterase activity.

Examination of sera from patients suffering from various diseases showed a difference in the values for the choline esterase which was still greater than that observed in normal individuals.

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<sup>1</sup> In this review of the literature no attempt is made to convert the units employed in the different investigations into the unit adopted by the present author.

Extensive data of this kind have been published by Antopol and co-workers who examined 500 patients. Adopting a manometer technique which was a modification of that of Ammon they found in normals an average of 67.6, with extremes of 44 and 80 units, while their total material showed extreme values of 8 and 163 units. Of this material they laid particular stress on the values from 35 cases of untreated thyrotoxicosis, nearly all of them lying above the upper limit for normals. They found approximately the same to be true of the cases of untreated diabetes, at any rate in the more severe cases, while they occasionally found extremely low values in diseases of the liver, in anemia and in febrile states. A single case of nephrosis showed a high value, but inasmuch as thyroxin had been administered, the investigators did not feel that definite conclusions could be drawn from this result.

Vahlquist, who was particularly interested in the relationship between choline esterase and tributyrin esterase in serum, found that both enzymes exhibited parallel variations in a number of diseases. Thus the value for both were low in 5 cases of tubercular cachexia. In 7 patients with endocrine complaints, more especially thyrotoxicosis, he found that the choline esterase did not vary from the normal.

Mc George, employing a titrimetric technique according to Stedman, found in 132 patients values ranging from 0.5 to 6.5 of his units. In practically all of the diseases investigated the values were scattered throughout the material, and, in contrast to Antopol and co-workers, Mc George found a spreading of the thyrotoxicosex instead of a representation by high values only. In case of patients with hypertension and heart failure the values were also distributed throughout the material, and the same was found to be true in 3 cases of myasthenia. By studying the serum choline esterase from day to day, Mc George found large variations, which, however, always seemed to follow the changes in the clinical state of the patient.

Milhorat who, employing a similar technique, examined 109 sera, found a range from 0.24 to 4.74 units. He was especially interested in patients displaying low values, and found that these low values were always due to debility caused by cancer, chronic infections, uremia or severe malnutrition. In a few cases he studied these patients for a longer period of time, finding that fluctuations

of the serum choline esterase in all essentials agreed with the clinical state of the patient. In one case of severe malnutrition the choline esterase value rose simultaneously with an improvement of the patient, accompanied by an increase in weight. As a point of special interest may be mentioned that the material included 6 cases of myasthenia gravis, but here the values for the serum choline esterase were found to be scattered among those representing other diseases. 5 of Milhorat's patients died; of these, 3 were studied until the end, towards the last showing falling values for the serum choline esterase.

In an investigation of 270 cases Mc Ardle found, in adults, a mean value of 78 and a range from 51 to 121 units, while for children the mean was 105 and the range from 71 to 166 units. In his pathological material he constantly found, like Mc George, low values in case of liver diseases, so constantly that he was of the opinion that determinations of the choline esterase in serum might be adapted as a measure of liver function. The very lowest values were in acute hepatitis when oedema occurred simultaneously, due to low serum albumin. Mc Ardle was unable, however, to give any explanation of these low values.

The conditions in anemia have been investigated, first of all, by Sabine who found reduced plasma choline esterase in all cases with less than 2.27 Mill. red blood corpuscles, or when the hematocrit value was below 25%. During treatment a pronounced rise in the plasma choline esterase was observed. In the cases of pernicious anemia on induced remission the values were found to be normal.

In addition to these more extensive investigations the literature contains a number of papers primarily dealing with the diseases in which one would expect changes in the choline esterase, not only in serum, but more especially in other places. Here the interest has first of all been focused on myasthenia gravis and myotonia congenita. Knowing that it is possible, at least temporarily, to improve the muscular function in myasthenia by means of pilocarpine, which specifically inhibits the choline esterase, it would seem natural to assume that an increased esterase activity will occur in this disease, at any rate in the muscle plates. It might therefore be expected that this increase would be reflected in the serum. The results of these investigations, however, do not carry much conviction. Thus Hicks and Mc Kay found increased serum choline esterase in 3 cases,

while Stedman and co-workers and Pichler found values lower than normal, and Poncher and Wade, like Milhorat and Mc George, found no deviations from the normal.

In myotonia — a disease showing a reaction to a number of pharmacological substances which is directly opposite to that of myasthenia — one would expect to find low values. But here too, Poncher and Wade found no deviation of the values from the normal. The only indication that the serum choline esterase level nevertheless is of some significance is an observation by Milhorat. He found that one of his patients, showing an especially low value of serum choline esterase, just as in myotonia developed a local muscle contraction, lasting about 6 seconds, at the point where the muscle had been struck with a percussion hammer. Two other patients whose serum choline esterase was equally as low did not present this phenomenon, however.

Conditions in allergic diseases, especially asthma, have also attracted attention. In the more extensive investigations, however, nothing was discovered that deviated from the normal, though Albus in a case of allergy found a value which was lower than in his only control, and Vahlquist, in asthma, found values somewhat lower than normal.

In hemorrhages, v. Verebely, like Antopol and co-workers, found a fall in the choline esterase, followed by a rapid rise. A fall occurs after an operation, especially when accompanied by cardiac and vascular complications. Low choline esterase values are also found in severe tuberculosis (Cattaneo, Scoz and Cattaneo) and in severe infections (Dikshit and Mahal).

It will be seen from this review of the literature that even though there are several points on which the majority of authors agree — like for example the wide variations among different individuals, and the low values in diseases of the liver, in anemia and in cachectic states — it is nevertheless impossible on the basis of the review to form a picture of the significance of the serum choline esterase, and of the conditions which are determining for the amount of esterase in serum. It would therefore seem reasonable to submit these problems to a new investigation.

*Technique.*

The gasometric technique employed differed but little from that described by Ammon.

Warburg's manometer apparatus was used, equipped with reaction vessels, each with a side branch. In most of the experiments the volume was 17 ml, in some 32 ml. The temperature of the thermostat was 38°.

The reagents included: Bicarbonate Ringer solution: Prepared from 100 ml of 0.9 % NaCl, 2 ml of 1.2 % KCl, 2 ml of 1.76 % CaCl<sub>2</sub> (hydrous) and 20 ml of 1.26 % NaHCO<sub>3</sub>. Substrate solution: 4 % acetylcholine chloride (Heyl & Co.) in bicarbonate Ringer solution. Enzyme solution: 1.25 % serum in bicarbonate Ringer solution.

Procedure: Blood for the determinations received no addition, and no consideration was given to the meals of the subject; the samples were usually taken in the forenoon. After coagulation the serum was removed and stored in the refrigerator at + 2°, at which temperature the esterase kept well, as shown by table 1.

Table 1.

Permanency of Serum Choline Esterase at + 2°

Days .....	0	1	2	3	5	7	14	22	35
Choline esterase units .....	57	57	58	57	57	58	58	57	56

The 1.25 % serum solution was prepared by transferring, with the aid of a micro-pipette according to Linderstrøm-Lang and Holter, approximately 30 ml of serum to a Ringer solution which was measured by means of Krogh's syringe, the latter being standardized against the micro-pipette so that the final concentration of the serum became 1.25 %. 2 ml of this solution were placed in the main body of the reaction vessel, with 7.5 ml of acetylcholine chloride solution in the side branch. The vessels were connected to the manometers, and a mixture of 5 % CO<sub>2</sub> and 95 % N<sub>2</sub> was led through. The vessels were then placed in the thermostat where they were shaken 80 to 100 times per minute.

The liquids were mixed 15 minutes later, and the readings began after an additional 5 minutes, with one reading every 5 minutes up to 30 minutes. 2 ml of Ringer solution and 0.5 ml of acetylcholine chloride were introduced into the thermobarometer in order

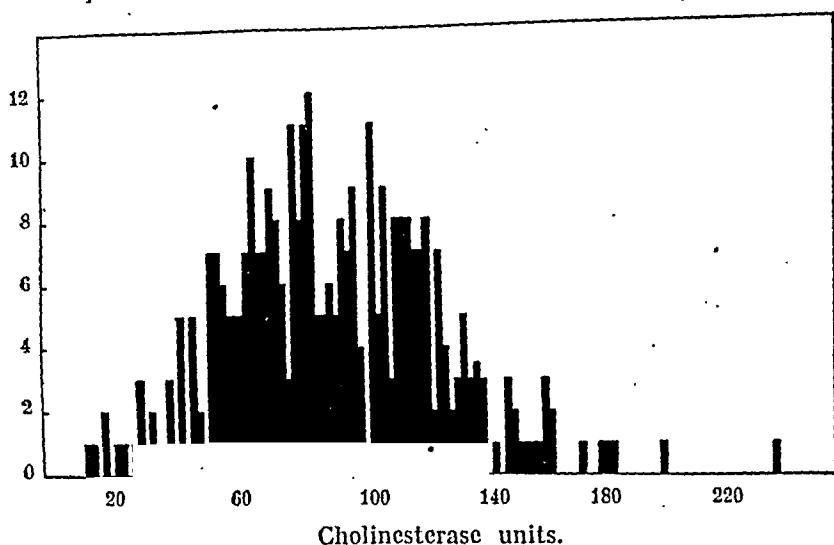


to compensate for the spontaneous hydrolysis. The final concentration in the analysis would then be 1% serum and 0.8% acetylcholine chloride. Under these conditions the reactions were linear, even in case of the stronger sera.

As unit for the choline esterase is used the volume in cmm of  $\text{CO}_2$  which under these conditions is liberated in the course of 1 hour. The mean error of this determination is 1.02 units, corresponding to 2 %.

### *The Author's Own Data.*

The material comprises about 500 determinations of serum choline esterase in 371 individuals. It includes both healthy subjects and hospitalized patients, and is distributed among 158 men, 181



The distribution of serumcholinesterase in 371 investigated sera.

Fig. 1.

women and 31 children, of which 19 are newborn. The distribution of the values is shown in fig. 1, with 14 units as the lowest, 241 units as the highest value, and a mean of 97 units. The material, though, is somewhat displaced in favour of the lower values, since the last 200 determinations are selected with a view of obtaining as many low values as possible.

### *Normal Individuals.*

For the purpose of elucidating conditions in normals, a material of 48 determinations has been collected, comprising 26 men and

24 women (the first classes in table 4). Like earlier investigators, the present author finds a rather considerable range of values, the extremes being 57 and 184 units, with a mean of 104. To this should be added the investigations on the placental blood which show a mean of 77, with extreme values of 58 and 115 units.

While there is thus a considerable variation among the different sera, the individual shows no variation during a 24 hour period, as will be seen from table 2. Over a longer period, however, distinct variations are found, as shown in table 3.

Table 2.

Diurnal Fluctuations of Serum Cholin Esterase.

Test No. ....	1	2	3	4	5
Fasting .....	43	86	75	99	123
12 noon .....	48	86	74	103	122
3 p. m. ....	45	83			

Table 3.

The Fluctuations of the Choline Esterase over a Longer Period of Time.

No. 1. Date .....	19. VI	3. VII	5. VII	8. VII	22. VII		
Choline esterase .....	73	80	62	64	43		
No. 2. Date .....	16. I	26. I	5. II	19. II	26. II	22. III	18. III
Choline esterase .....	32	40	49	54	57	77	91
No. 3. Date .....	5. I	9. I	15. I	19. I	24. I	26. I	29. I
Choline esterase .....	155	121	89	99	106	86	106
							5. II
							111

*Pathological Cases.*

As expected, a substantially larger variation is found in the pathological material than in the normal, a variation which is marked by the presence of some especially low values and others which are rather high. The extremes are 14 and 241, with a mean of 97 units. The complete material is recorded in table 4, arranged according to the chief diagnoses.

The combined material shows no demonstrable difference between the values for the two sexes, the mean being 95 for men, with a standard deviation of 36.6, and for women 87 with a standard deviation of 34.1 units. In case of normals, however, the values for the men seem to be somewhat higher (117 units) than those for the women (87 units), but the difference is not statistically valid because of the relatively small scope of the material.

In contrast to what is otherwise found in more extensive investigations on serum choline esterase, the author's data seem to show some difference between the values for the various age-classes. According to table 5 somewhat higher values are found, as mean and maximum, in the individuals above 75 years of age, while the values are found to be alike in the younger year-classes. A deviation is encountered, however, since both the mean and the upper extreme for the placental blood definitely show lower values in comparison with the values for adults. A similar observation was made by Ammon and Voss and by v. Verebely, the latter adding, however, that he always found lower values in the child than in the mother.

Table 4.

The Distribution of the Serum Choline Esterase in the Collected Material.

Normal men .....	150	149	146	145	142	140	139	136	131	130	128
	123	120	117	116	115	111	101	93	90	90	88
	86	84	77	65							
Normal women .....	184	133	129	122	113	110	95	88	84	81	80
	77	77	76	76	75	75	75	70	70	65	58
	57										
Newborn .....	115	105	97	90	90	85	81	78	77	75	71
	70	68	67	67	65	64	62	59	58		
Diseases of the heart:											
Hypertens. art. ....	242	201	169	143	122	104	91	83			
Degeneratio myoc. ....	196	160	146	139	134	126	126	123	122	118	118
	114	114	111	110	105	102	91	89			
Arteriosclerosis .....	146	145	123	122	121	111	101	100	94	78	62
	57	56									
Mb. cordis, comp. ....	104	80	74	72	68						
Mb. cordis, incomp. ....	107	102	89	53	50	30	20				
Phlebitis .....	102	85	32								
Diseases of the lung:											
Pneumonia .....	92	89	88	86	85	77	51	46	42		
Pleuritis .....	128	96	84	76							
Asthma bronch. ....	102	97	72								
Bronch. chron. ....	112	68	62								
Other lung diseases ....	163	115	71								
Diseases of the stomach:											
Gastritis and ulcer .....	139	113	108	91	90	85	77	70	69	65	57
Colitis + ulcerous colitis ..	167	119	111	85	25						
Other stomach diseases ....	140	114	102	79	78	69	34				
Diseases of the liver:											
Hepatitis ac. ....	61	56	50	47	43	41					
Hepatitis chron. ....	92	67	70	50							

Cholelithiasis .....	167	157	147	111	96	87	75			
Other liver diseases .....	51	14								
Diseases of the blood:										
Anemia pern. ....	121	120	107	105	88	70				
Anemia simplex .....	100	88	36							
Hemorrhagic diatesis ....	133	120	116	73						
Diseases of endocrine glands:										
Diabetes mellitus.....	166	156	155	133	129	111	105	102		
Adipositas .....	134	93	88							
Graves' disease .....	120									
Myxoedema .....	120	67								
Diseases of the joints:										
Polyarthrititis .....	143	139	129	104	96	86	86	63	60	
Other dis. of the joints ..	168	145	124	111	110	101	95	86	75	59 58
Diseases of the kidneys:										
Nephritis .....	137	128	120	89	72					
Nephrosis .....	186	100								
Nephrosclerosis .....	128	104	90	83						
Other dis. of the kidneys ..	145	141	115	98	74	64				
Uremia .....	56	53	49	32						
Diseases of the nervous system:										
Myotonia atrophica .....	120	95								
Amyotonia congenita.....	125									
Amyotrophic lateral sclerosis	118	107	54							
Progressive muscular										
dystrophy .....	115	91								
Hemiparesis .....	188	132								
Cerebral hemorrhage .....	144	139	124	100	100	91	85	85	81	78 38
Other nervous diseases: ..	176	168	127	124	122	96	90	89	77	
Mb. mentalis .....	129	118	107							
Cancer, independent of loca-										
lization .....	99	85	82	81	78	71	63	61	57	47 44
	43	33								
Other diagnoses .....	134	133	120	115	115	114	112	98	93	88 87
	75	74	68							

Table 5.

The Relationship Between Age and Serum Choline Esterase Expressed in Percentage of Total Material.

Age	Choline esterase units				
	0—50	50—100	100—150	150—200	Above 200
0—1 .....	0	6	0.6	0	0
1—24 .....	0	5	7	0.3	0
25—49 .....	1.6	13.3	9	0.6	0
50—74 .....	4.3	15.9	15.9	2.3	0
Above 75 .....	1	5.3	9.3	2	0.6

*The Connection Between Diseases and Serum Choline Esterase.*

While the values for the serum choline esterase in most of the diseases are scattered throughout the material, we nevertheless find some diseases which show a definite trend towards values lower than normal, or at any rate values which fall below the mean. Thus, as a rule, we find much reduced values in case of liver diseases. The 6 cases of acute hepatitis included in this material give values between 30 and 61 units. An isolated case of coma hepaticum, presumably due to numerous liver metastases from mammary cancer, shows the lowest value in the whole material, viz., 14 units. The values in liver cirrhosis are somewhat higher than in acute hepatitis, 5 of the cases examined giving values between 92 and 47 units, but all of them below the mean value. In contrast to this we find that the values in the 7 cases of cholelithiasis lie rather above the mean. These findings correspond to earlier results obtained by Antopol and co-workers and by Mc Ardle.

Low values, but not so definitely low as in the diseases of the liver, are found in anemia, especially where the anemia is uncompensated, as is the case in pernicious anemia in recession. Reduced values are also found after acute hemorrhages. Thus 7 cases of posthemorrhagic anemia, most of them due to hemorrhages in the gastrointestinal tract, give values ranging from 57 to 113 units, so that the reduction here is not so pronounced as in the more chronic anemias.

In cancer the values are in most cases found to be strongly reduced. Thus between 99 and 33 units are found in 13 patients, with a trend towards especially low values when hemorrhage or anemia occurs simultaneously, 4 patients within this category showing values between 33 and 71 units. Metastases in the liver undoubtedly occurred in several of these cases, though no symptoms thereof were found in any of them.

Values of 30, 50 and 53 units are found in 3 cases of very severe heart failure with oedema and ascites, one of them, at any rate, also showing liver damage.

In more severe infectious diseases we also find a trend towards lower values. Thus in 9 cases of pneumonia the values lie between 92 and 37. In pleuritis, however, no reduction is found, 4 cases showing values between 128 and 76 units.

Especially low values can be found in kidney diseases with reduced kidney function. In the 13 cases examined, values between 137 and 32 units are found. Of these, the lowest values are in 4 cases of uremia.

The findings may be summarized as follows: The serum choline esterase is found to be reduced or low in diseases of the liver parenchyma, as well as in diseases which essentially affect the general condition, especially diseases which are accompanied also by anorexia.

While the author's results and those of the earlier literature thus are found to be in good agreement with respect to the low values, the same is not entirely true as far as the higher values are concerned. Here the author's data show an absolute predominance of arteriosclerotic heart disease and hypertension, a circumstance which presumably is responsible for the higher values which the author finds in the individuals older than 75. The explanation may be that some of the present data have been obtained at a home for the aged, so that it includes a relatively large number of hypertensive patients who are otherwise well.

The present data throw no light on the high values in thyrotoxicosis, described by Antopol, since the only patient with Graves' disease shows 120 units, thus normal value. In 2 cases of myxoedema the conditions are found to be entirely normal. Like Antopol, the author finds high values in cases of diabetes, in the present material ranging from 166 to 102 units.

The 2 cases of myotonia investigated both show normal values. No case of myasthenia is included in the material.

The conclusion must then be that the serum choline esterase shows a very wide range of the values, both in case of healthy and diseased individuals, apparently governed by no special rule. Two groups, however, can be picked among the patients. One group with low values comprises patients suffering from diseases of the liver and a number of diseases accompanied by a poor general condition of the patient. The other group shows high values and comprises first of all patients with hypertension, but also diabetics. It should be possible on this basis to arrive at a better understanding of the large differences which are found among the individuals examined.

## Summary.

On the basis of the literature and the author's own investigations comprising more than 400 individuals a description is given of the fluctuations of serum choline esterase under normal and under pathological conditions. It is pointed out that the spreading is large in case of normals, and even more pronounced in the pathological material. The pathological cases are discussed, with special mention of the low values. These low values are in particular found in patients suffering from diseases of the liver, anemia, cancer and malnutrition. Simple investigations on the choline esterase will hardly lead to new results, but the diseases mentioned may perhaps prove useful in finding a common factor for the enzyme variations.

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## The relationship between serum choline esterase and serum albumin.<sup>1</sup>

By

MOGENS FABER.

(Submitted for publication November 27, 1942).

In an earlier paper (Faber) it was shown how the serum choline esterase activity varied strongly from individual to individual, even in normals, and how, in a number of diseases, there was a pronounced tendency for the esterase value to adjust itself at a level which might be considered characteristic for the disease in question. It is now natural to ask whether it is possible to give any reasons for this variation under both normal and diseased conditions.

A closer examination of the cases which exhibited low values of the serum choline esterase — patients with damaged liver, severe anemia, cancer, or severe heart failure — gave as the sole phenomenon in common that in all these cases a serum albumin concentration could be expected which was lower than normal.

Thus it is very well known that liver cirrhosis is accompanied by reduced albumin in serum — as stated by Snell and co-workers, Myers and Keeser, Salvesen, and Foley and co-workers. The reduction is especially pronounced in the more severe cases with ascites. The albumin content of serum also shows a fall in other diseases of the liver where the liver parenchyma is damaged. It can be especially pronounced in hepatitis, where, in severe cases, oedema may be observed due to the low concentration of serum

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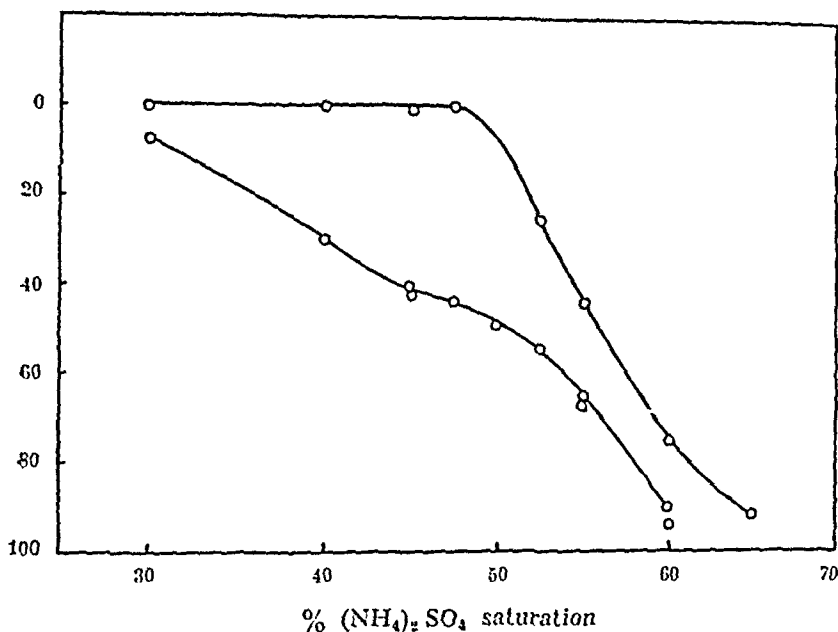
<sup>1</sup> Aided by a grant from Nordisk Insulin Fond.



tion. With this in mind the present author conducted a series of experiments to determine the behavior of the choline esterase during the fractionated precipitation of the serum proteins by means of ammonium sulphate.

One of these experiments is recorded in fig. 1. It is here seen how the choline esterase is not precipitated with the globulin fraction, practically all of it still being in solution at the point of half-

% protein  
precipitated



The upper curve shows the salting out of the choline esterase with  $(\text{NH}_4)_2\text{SO}_4$ . The lower curve shows the simultaneous salting out of the serum proteins.

Fig. 1.

saturation, thereupon being rapidly precipitated at increasing addition of salt. It seems, however, that a relatively large amount is left, corresponding to the albumin fractions which are the most difficult to precipitate.

With some slight modification the method of Henriques and Klausen was used in the determination of the serum proteins. A semi-micromethod was adopted, incorporating a micro-Kjeldahl determination which required only 1 mg N instead of the approximately 5 mg necessary in the original method. For details, see Henriques and Klausen.

The protein was estimated as N multiplied by 6.25, the nitrogen having been determined according to the method of A. C. Andersen and Norman Jensen. For details, see paper by these authors.

In all instances double analyses were made, and it was required that each pair of results, expressed as percentage of protein in serum, should not differ more than 0.15 % from one another. When

Total Serum  
protein %

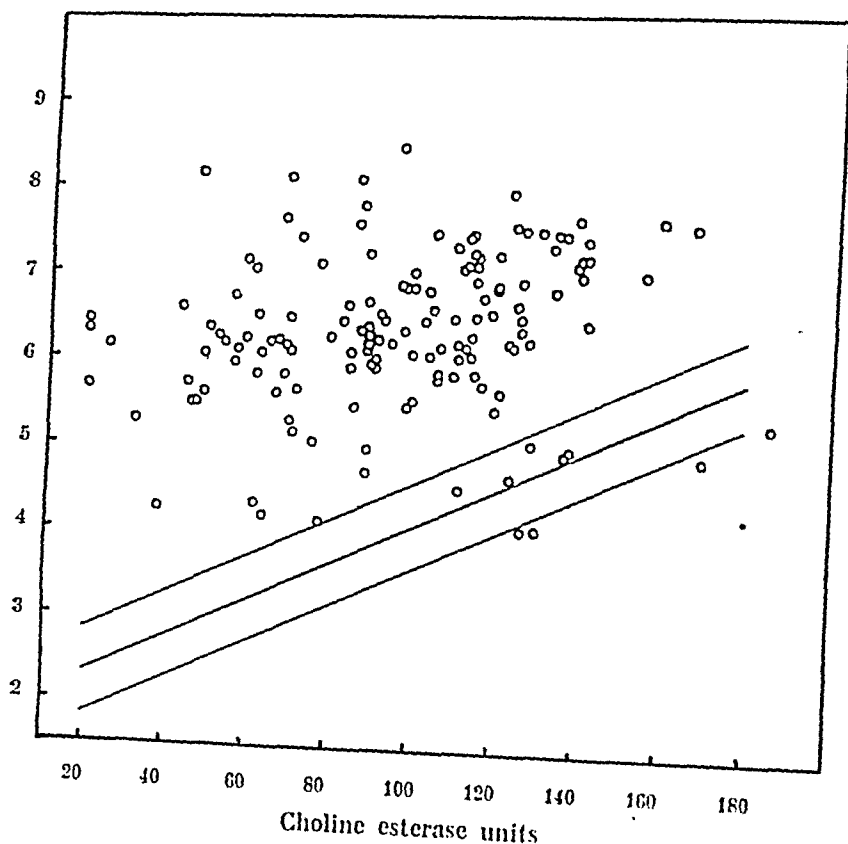


Fig. 2.

the deviation exceeded this figure the analyses were repeated. In 50 consecutive determinations the mean deviation was found to be 0.067 % in case of total protein, and 0.057 % in case of albumin, which corresponds to 1—1.5 % of the total serum protein and about 2 % of the total serum albumin.

The results of the investigations are recorded in figs. 2, 3 and 4. As basis the first determination made in case of each individual is used. All persons examined are included, with exception of the patients with albuminuria who will be considered separately.

As seen from fig. 2 there is a slight indication of a correlation between the concentrations of choline esterase and protein in serum. Fig. 3 shows that this correlation is not due to the presence of globulin — on the contrary, the correlation becomes unquestionable when the globulin is removed from the total protein so that only the albumin remains, see fig. 4. In all cases it is found that the choline

Serum  
Globulin %

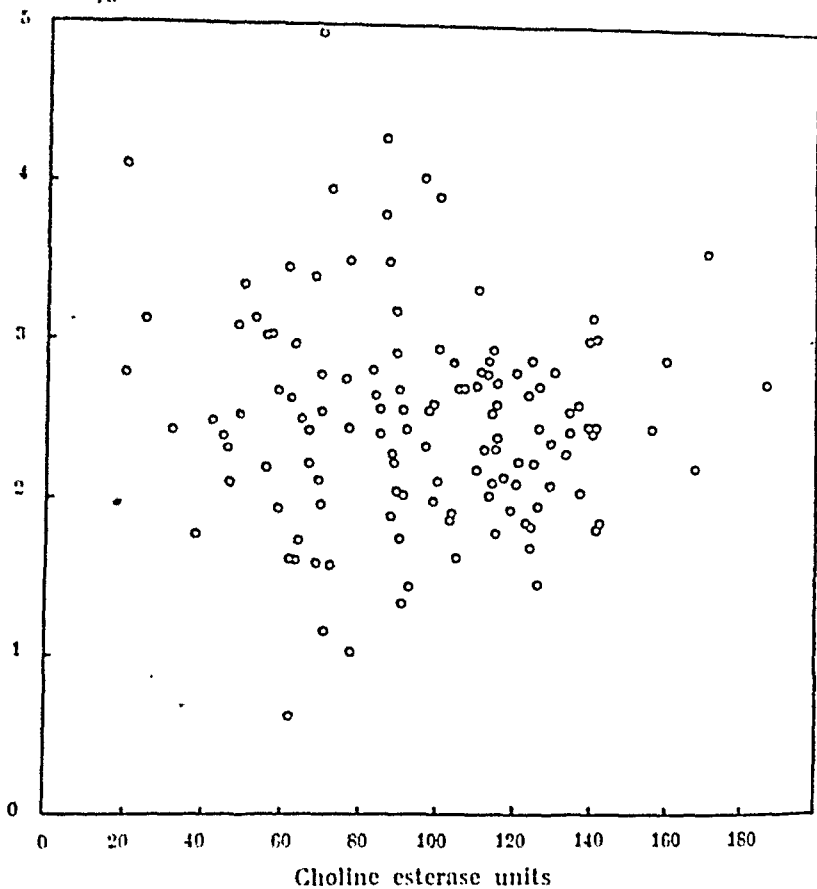


Fig. 3.

esterase content of the serum is low when the albumin is low, and, in nearly all cases, that it is high when the serum albumin content is high. We thus find a rising choline esterase concentration with a rising albumin concentration in serum. Unfortunately, the material does not include patients with extremely reduced serum albumin without albuminuria occurring at the same time, the lowest value in the material being 2.10 %. It is therefore impossible to state how the serum choline esterase will behave under these circumstan-

ces, and a complete curve cannot be drawn on the basis of the available material. Moreover, the difficulty of obtaining such a curve is increased by the quite considerable spreading of the results. A calculation has therefore been made of the simplest curve that may be drawn among the available points in such a way that it gives to each point the smallest possible deviation from the mean.

Serum  
Albumin  $\frac{3}{4}$

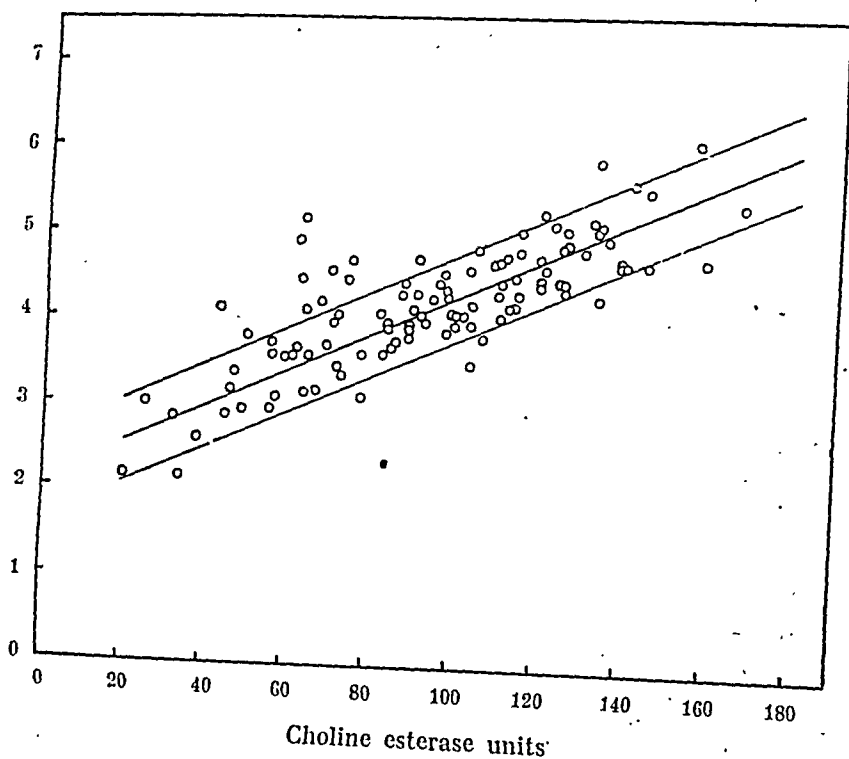


Fig. 4.

The result is a straight line with the formula: Choline esterase =  $45 \cdot \text{albumin} - 95$ . This line is traced in the figures, but only within the range of the available determinations in order to avoid any suggestion of its possible course in the regions where no determinations have been made.

According to Brochner-Mortensen, the normal value for serum albumin, determined by the method of Henriques and Klausen, is from 3.6 to 5.3 %. The present material includes 12 normals where determinations are made of both albumin and serum choline esterase in serum. The values are here, for albumin, between 4.53 and 5.31 %, and for choline esterase between 111 and 149 units. In all in-

stances but one these values are located close to the representative curve, the average line, in fig. 4.

Though the majority of all values in fig. 4 are located close to this average line, there are some deviations which occasionally are quite large, and it should be of interest to find an explanation of these deviating values. An arbitrary limit of 0.5 % has therefore been fixed, and two lines drawn parallel to the average line, so that all points within these limits represent a variation in serum albumin of not more than  $\pm 0.5$  %. The values from 88 of the cases are found within these limits, while 21 values lie without. The journals of the cases where the values fall outside the limits have been carefully studied with a view of finding a correlation between the nature of the variation and the clinical findings.

It is then found that of the 13 determinations which lie above the upper limit, 9 represent patients in a state of clinical improvement. This means that the patients either show increase in weight, rising hemoglobin percentage in anemia, or falling icterus index in diseases of the liver. Only 1 of the 13 patients is in a declining state of health, the remaining 3 are clinically at rest, without improvement or aggravation. The opposite is found to be true of the 8 patients represented by points below the lower limit, 6 of them being in a state of declining health, 2 of them at rest, and none in a state of improvement.

These findings show that the wide spreading in fig. 4 is not a random one. Values above the upper limit are those of patients who are plainly getting well, and presumably for this reason show an increase in serum albumin concentration which is found to be relatively larger than the increase in serum choline esterase concentration. The result is therefore a displacement of the equilibrium ratio between albumin and choline esterase in serum in favour of the albumin. In contrast to these values, those below the lower limit represent patients in a state of declining health, as a rule because the disease is in its first stage. On this account the values for the serum albumin are decreasing, while the simultaneous fall in serum choline esterase values proceeds at a slower rate. The result is that the equilibrium ratio is displaced in favour of the choline esterase. It thus seems that the serum choline esterase does not always run parallel to the serum albumin, but that the choline esterase will lag behind when the variations are rapid.

The correlation established here by an analysis of a number of individual determinations is also found in repeated examinations of the same patient. Case 1 is illustrative of patients in whom there is no change of the serum albumin, which, as will be mentioned later, must be supposed to be the primary factor in this relationship.

All graphs accompanying the cases in the present paper show not only the variations in serum choline esterase and serum albumin, but also the deviations from the average line in fig. 4. These deviations are recorded at the top of the figure and expressed in percentage of serum albumin.

### Case 1.

A man aged 59 years.

Diagnosis: Cancer ventriculi.

From the journal: Earlier history of good health. Ill 2 months with epigastric pain; no vomiting or melaena. The patient had lost 7—8 kg in weight during the last year.

Examination upon admission showed nothing except anemia.

Weight 60.5 kg. Hemoglobin percentage 52. Feces + blood reaction during entire stay in hospital.

While in hospital the patient suffered from continued oppression of the epigastrium with nausea and vomiting. He gained 0.6 kg, however, and Hb rose to 75 %; otherwise no change. Discharged on continued ambula-

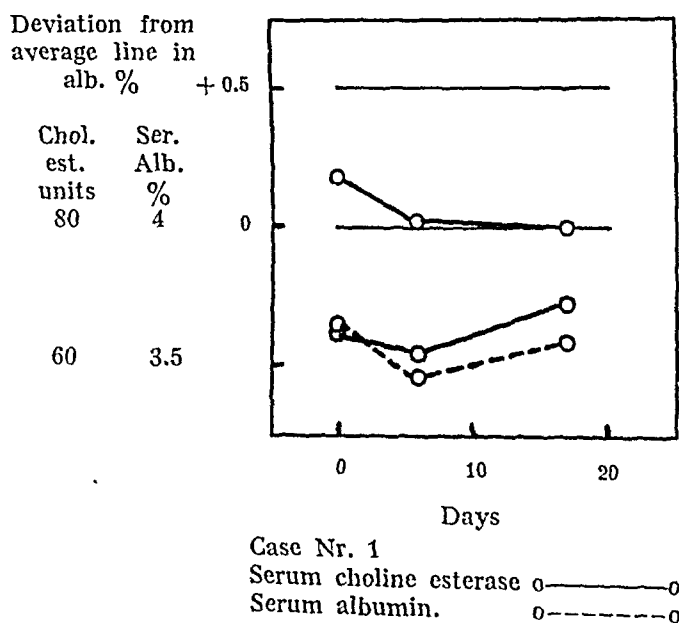


Fig. 5.

tory treatment, but admitted once more on account of hematemesis, and died 8. I. 1940.

Determinations of the protein and choline esterase of this patient are recorded in fig. 5.

Comment: A patient whose condition during the period of examination was changed but slightly showed no substantial changes in the albumin concentration nor in the concentration of serum choline esterase.

Conditions in patients who are in a state of improvement are seen from the following two cases:

### Case 2.

A woman aged 66 years.

Diagnosis: Phlebitis extr. inf. dext. Infarctus pulm. Colipyuria.

From the journal: Became ill 2 weeks before admission, with pain, reddening and swelling of the right leg. Typical phlebitis of the right leg with oedema and soreness was found at the time of admission. The examination showed nothing abnormal except extra systoles. Sedimentation reaction, 30. XII, 9 mm, 15. I, 15 mm.

During hospitalization conditions improved.

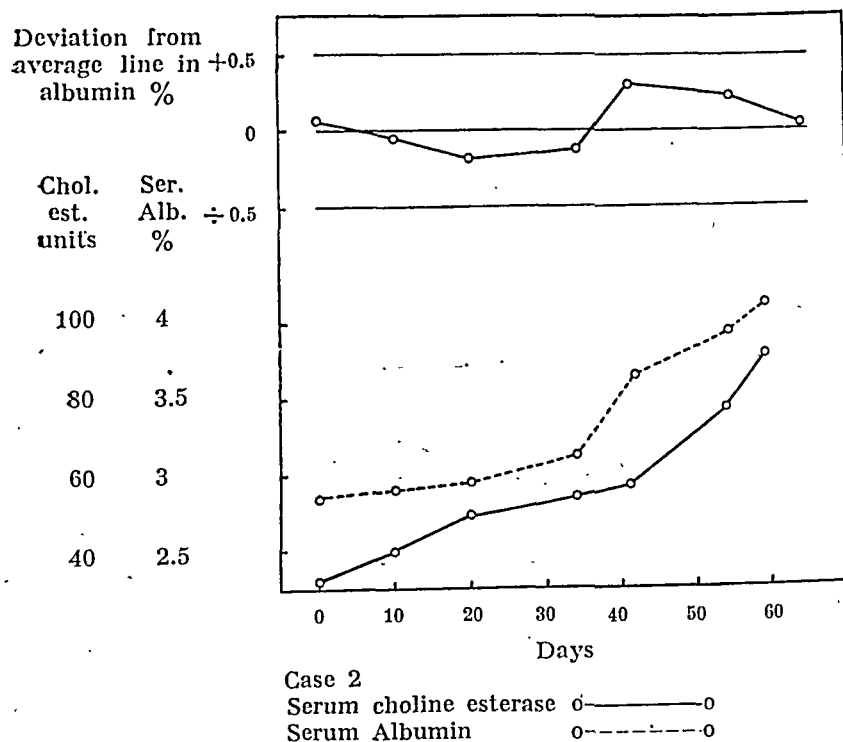


Fig. 6.

Reddening and oedema of left leg were discovered on 12. I. On 22. I she had an attack of right-handed infarction of the lung. The temperature dropped slowly and was not normal until 23. II. The oedema and soreness diminished gradually. On 24. II there was still 1—1.5 cm swelling of the right leg. There were no longer symptoms of phlebitis.

Determinations of the protein and choline esterase of this patient are recorded in fig. 6.

Comment: We have here a patient whose serum choline esterase activity, during an acute febrile disease and presumably before admission, had dropped below the usual level. In the hospital she was observed during the period of improvement. In this period there was a constant increase in the concentrations of both serum albumin and serum choline esterase. During the increase these values were found to be located rather close to the average line of fig. 4.

### Case 3.

A woman aged 63 years.

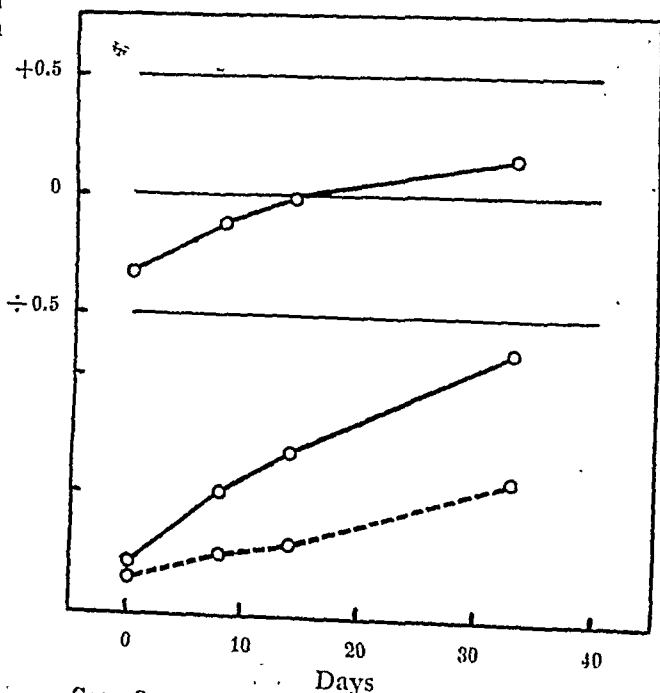
Diagnosis: Acute hepatitis.

From the journal: The present disease began about 1 month before admission with leftsided abdominal pains. The patient was tired, with

Deviation from  
average line in  
alb. %

Chol. Ser.  
est. Alb.  
units %

90 3.75  
70 3.25  
50 2.75



Case 3

Serum choline esterase —○—○—○  
Serum albumin - - -○- - -○- - -○

Fig. 7.



loss in weight and poor appetite. The temperature was about 38°. Icterus was observed, feces were light and the urine dark. Nothing except icterus was found at the time of admission.

Hemoglobin percentage 95. Icterus index 135. Weight 58.5 kg.

Steady improvement during stay in hospital. Icterus decreased, feces coloured after 1 week. In 3 weeks the icterus index was 45, the liver could be felt a couple of centimeters below the curvature. In 5 weeks from admission the icterus index had dropped to 21.

Determinations of the protein and choline esterase of this patient are recorded in fig. 7.

Comment: During the recovery from an acute hepatitis a steady rise was observed in the concentrations of both serum albumin and serum choline esterase. This rise, however, was considerably more rapid in case of the albumin than in case of the esterase. The ratio between the two therefore increased substantially more than one would expect from the average line in fig. 4. At the last determination, though, there seemed to be a tendency towards a reduction in the predominance of the albumin rise.

#### Case 4.

A woman of 54 years.

Diagnosis: Morbus cordis mitralis. Insuff. cordis. Ascites.

From the journal: In 1939 the patient was at home with febrile bronchitis. In September 1939 admitted to hospital on account of stenosis et insufficiensia mitralis. Admitted once more in January 1940 with the same ailment plus ascites. Discharged after having lost 6 kg in weight. Admitted once more 15. III. 1940. Had been completely unable to work at home. The last 2 days before admission the temperature was 40° with some expectorate.

At the time of admission orthopnoeic with light cyanosis. Stasis of the lungs and ascites were observed, and the liver extended below the curvature. The temperature dropped during the first days and the patient felt better. On 28. III the temperature rose again, and there was ample frothing expectorate as in oedema of the lungs. During the time following the condition grew worse, the oedema increased. The cyanosis was almost universal on 26. IV. Strong nausea and vomiting set in, so that the treatment had to be suspended; death occurred on 12. V.

Determinations of the protein and choline esterase of this patient are recorded in fig. 8.

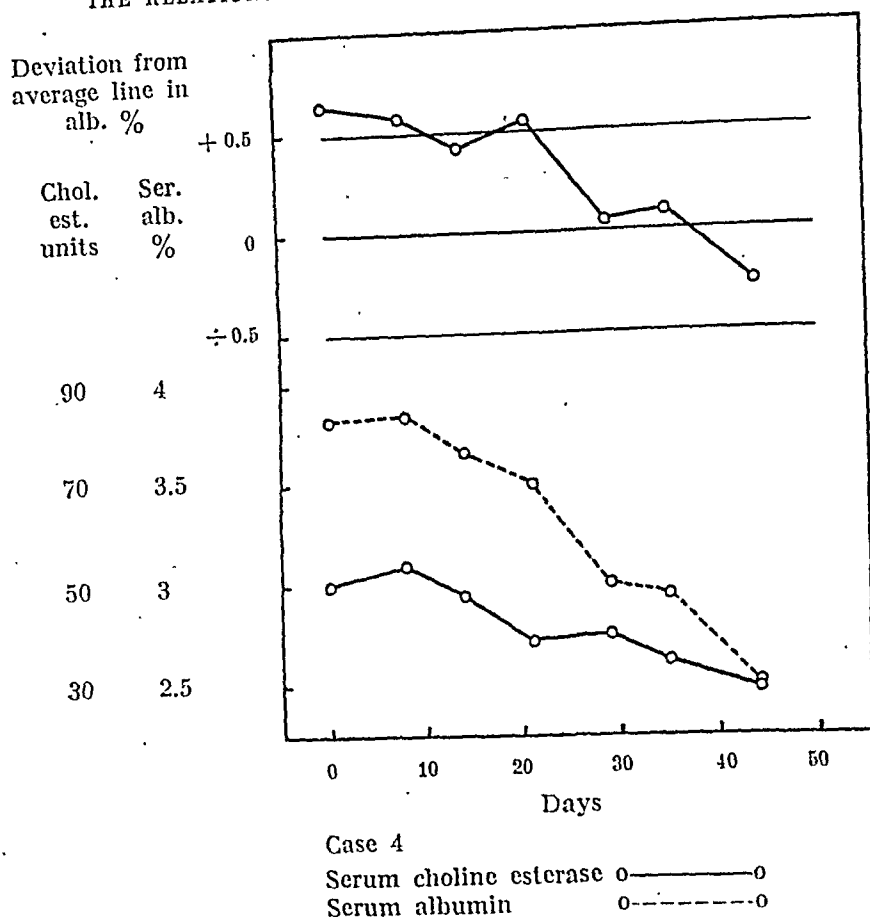


Fig. 8.

Comment: This patient, who was, admitted with heart failure, was studied almost until time of death. At first there was some slight improvement. During this time there was no change in the concentrations of serum albumin or serum choline esterase. Then conditions were aggravated, and during the whole of the ensuing period there was a steady falling off of the concentrations of both serum albumin and serum choline esterase. In the former, however, the fall was substantially more rapid than in the latter, to that the ratio between the two concentrations was seen to fall more rapidly than one would expect from the average line in fig. 4.

As the last case will be described that of a patient who, during the period of observation, showed both improvement and aggravation, with resulting variations of the concentrations of serum albumin and serum choline esterase.

Deviation from  
average line in  
alb. %

Chol.  
est.  
units

Ser.  
alb.  
%

÷ 0.5

÷ 1

150

5

130

4.5

110

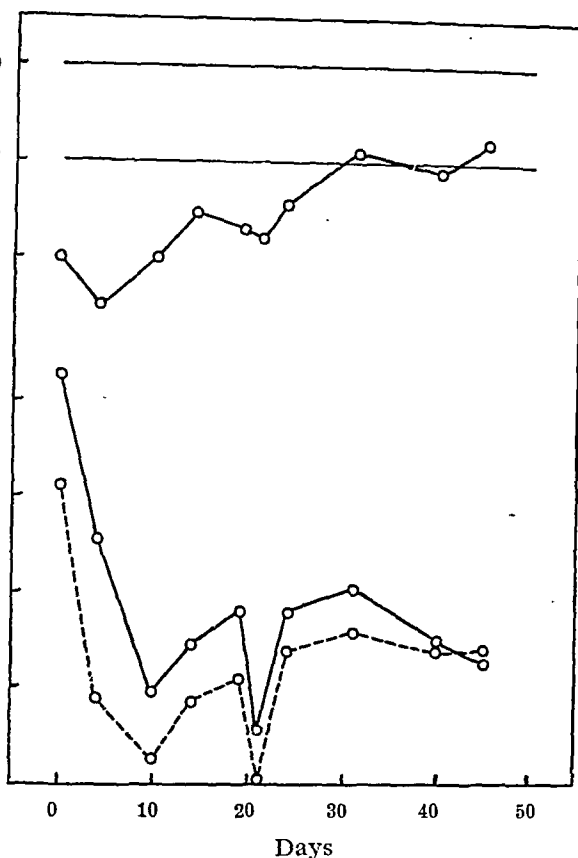
4

90

3.5

70

3



Case 5

Serum choline esterase o—o

Serum albumin o---o

Fig. 9.

### Case 5.

A woman of 77 years.

Diagnosis: Degeneratio myocardii. Insuff. cordis. Diabetes mellitus.

From the journal: In later years the patient was dyspnoeic, but this condition had not been a real inconvenience until the last 6 months. Stenocardic attack occurred about 1 month before admission, with several attacks during the last 2 weeks. Diabetic for 7 years, treated on diet and insulin.

Physical examination showed nothing of interest.

Hemoglobin percentage 95. Urine + S.

The health was good during the first few days, then followed several days with repeated stenocardic attacks, no action of nitroglycerin. Attacks of cardiac asthma occurred on one occasion. The next few days the patient was somewhat dyspnoeic, with slight crural oedema. On 24. I again feeling poorer with precordial oppression, appearing quite tormented and dyspnoeic. Oedema rather spreading to femur. When weighed on 6. II for the

second time since admission the patient had gained 14 kg. Ascites was now found, in addition to the extremely oedema. During the following time the oedema decreased somewhat, and the patient was discharged according to own wish.

Determinations of protein and choline esterase of this patient are recorded in fig. 9.

Comment: This patient was admitted to the hospital with acute aggravation of heart disease complicated by diabetes. Immediately upon admission there occurred a violent drop of the serum protein, affecting only the albumin fraction. The drop was accompanied by a slower fall of the serum choline esterase. Then an improvement set in, reflected in the rising concentrations of serum albumin and serum choline esterase. The improvement was interrupted, however, during the acute heart attack on 24. I when there occurred a renewed fall in the concentrations of the serum albumin and the serum choline esterase. Then followed a continuous rise of the serum albumin concentration, as an expression of the improved condition of the patient, but the rise in the concentration of choline esterase was not quite of the same magnitude. Fig. 9 shows these variations of the ratio between albumin and choline esterase relative to the average line. When a fall is observed in the concentrations of albumin and choline esterase, the albumin is found to change more rapidly, so that the points representing the albumin/choline esterase ratio will recede from the average line. When the albumin concentration rises, however, these points will approach the average line and finally fall within the 0.5 % albumin limit.

These cases show how conditions vary in the individual patient. The results also show that the conclusions which may be drawn from single examinations of many patients may be freely applied to the conditions as we find them in repeated examinations of a single individual.

It must therefore be considered certain that serum will contain an amount of choline esterase which in its relationship to the serum albumin will follow the rules established here, so that in most cases it will be possible, on the basis of the serum albumin determination, to estimate how much serum choline esterase there is in a given blood sample.

## The Formation of the Serum Choline Esterase.

On the basis of these observations it should be possible to present an explanation of how serum choline esterase varies, and, at the same time to suggest its place of origin.

It is demonstrated that there exists a definite relation between serum choline esterase and serum albumin, and several explanations may be advanced to account for this phenomenon.

Thus it might be imagined that the choline esterase in serum always is bound to the serum albumin, in common with what is found in case of several low-molecular substances, as especially emphasized by Bennhold in regard to bile pigments for example, which are always bound to the serum albumin. This binding, however, differs in several respects from what is observed in case of the choline esterase. Thus there is no constant ratio between the bile pigment and the albumin in serum, since the amount of bile pigment which is bound solely depends on the amount of bile pigment present in serum and not on the amount of albumin, and since all bile pigment is bound to the serum albumin. Moreover, Vahlquist's experiments on the migration in an electrical field are in direct contradiction to this assumption, since he finds that the choline esterase migrates independently of the other proteins, in contrast to the bile pigments which in cataphoresis experiments migrate with the albumin.

Since both choline esterase and albumin must have a cellular origin, this origin might possibly be in the same organ. Nothing in the present data indicates that the two substances should have their origin in different organs. If that were so, diseases which attacked only one of these organs would produce a characteristic change in the equilibrium ratio between the two substances in serum.

Thus there is nothing to contradict that both the choline esterase and the albumin have their origin in the same organ. If, from the cells where the albumin is formed, there occurred, simultaneously with the secretion of albumin, a slight loss of choline esterase in an amount dependent on the amount of albumin liberated — one might almost speak of a leakage of choline esterase along with the albumin secreted — then an equilibrium ratio between the two substances would be established in serum. Plotting this ratio it would be expected, at varying amounts of choline esterase in the serum, that the points would be grouped around a straight line

through the zero point. This is not found to be the case, however, since the line we arrived at in fig. 4 does not point towards zero, but it may be presumed that this line represents a portion of a complete curve which may then pass through the zero point. Especially at higher values this curve shows a considerable displacement in favour of the choline esterase. This displacement must presumably be explained on the basis of the stability conditions in serum. The serum albumin seems constantly to be formed and again broken down, as shown by Schoenheimer, Ratner and Rittenberg, and under other conditions by Whipple and co-workers. The stability of choline esterase in serum is not known, but it seems to be quite considerable, at any rate in most cases. When the choline esterase is secreted into the serum together with the albumin, from the same cells and presumably in a rather constant ratio, the two substances will adjust themselves naturally to an albumin/enzyme ratio which, owing to the higher stability of esterase, will follow the rules mentioned above.

When a patient is in a state of recovery, and for that reason the albumin formation will be dominating in comparison with the simultaneous breakdown, we will in some cases find a displacement of the ratio between albumin and esterase, in favour of the albumin. Because of the higher stability of the enzyme in serum there will be found relatively more choline esterase in the serum than in the mixture which is secreted from the place of formation. The result is that at first, when there occurs an increased formation of both albumin and choline esterase, there will be a rise in the albumin values, receding from the average line, followed by a slower rise in the esterase values. This rise will not reach its maximum until the albumin rise is diminishing, and not until then will there develop a new state of equilibrium with values close to the average line.

The opposite will be true when there occurs a rapid drop in the albumin concentration, so that in this case we shall find a variation below the average line.

### The Origin of the Serum Choline Esterase.

On the basis of what is said in the foregoing it should be possible to suggest an organ in which the choline esterase is formed, and since all cases of liver disease, as already mentioned, are accompanied by

a low level of the serum choline esterase, it is tempting to suggest the liver as the organ in question.

This idea is also supported by the experiences gained with respect to reduced serum albumin in diseases without albuminuria and without nutritional disturbances. As mentioned, liver cirrhosis is usually accompanied by reduced albumin, and the like is found to be true of most acute or chronic liver damages, especially in severe acute hepatitis where the albumin concentration, as in one case cited by Mc Ardle, may drop to 0.7 %.

The idea is moreover supported by experimental investigations. Upon intoxication with phosphorus Henriques and Klausen found a pronounced drop in the albumin concentration as an expression of the injury to the liver, and Knutti and co-workers found similar results on intoxication with carbon tetrachloride.

It may thus be said that most facts indicate that the serum albumin is formed in the liver. In that case it follows that the serum choline esterase also must have its origin here. As previously mentioned, however, the circumstance that the formation of serum albumin and serum choline esterase is reduced in diseases of the liver is not in itself sufficient to explain the variations found in serum choline esterase.

It is therefore necessary to extend the investigations to include also a review of the conditions which, in addition to diseases of the liver and kidney, may cause variations in the serum albumin.

It has long been known that the so-called nutritional oedema in most cases is due to protein inanition with subsequent reduced formation of serum albumin (Peters and co-workers, Liu, Chu, Wang and Chung). This observation has been confirmed through the very beautiful experiments of Weech and co-workers. By keeping dogs on a diet deficient in proteins they were able to produce a fall in serum protein so that the dogs developed nutritional oedema in the course of about 100 days. They showed that the fall in serum protein solely involved a fall in the albumin fraction, while the globulin fraction remained unchanged. If now protein was added to the diet, the serum albumin rose immediately. Weech showed moreover, how there was a pronounced difference in the ability of the different proteins to form serum protein. Practically the same results were obtained by Whipple and co-workers in plasmaphoresis experiments on dogs.

Since the serum albumin is so dependent on the diet, it would be natural to expect the same to be true of the serum choline esterase, and this is actually found to be the case. As already mentioned, the author's data as well as the data of other investigators, show frequent examples of low values in patients with diseases associated with poor nutritional condition. The author's material shows for example values which are low in cancer, quite independently of

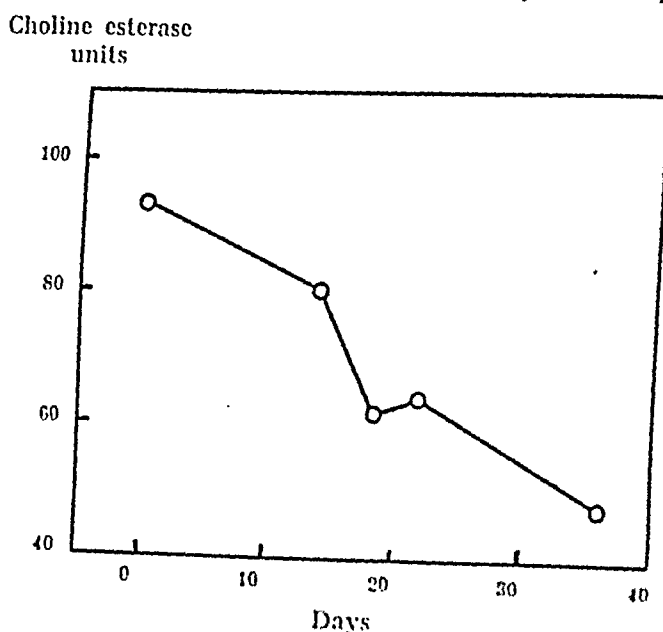


Fig. 10.

the localization. That a fall in the serum choline esterase activity may also occur in an otherwise healthy person is seen in fig. 10. Here we find a strong fall in the serum choline esterase concentration in the course of a month, simultaneously with a loss in weight of 5 kg while on a predominatingly vegetable diet. Unfortunately no determinations were made of the serum albumin in this case. About 6 months later the same person showed a choline esterase value of 124 units.

As shown by Weech's experiments, quite a long time is needed before there occurs a fall in the serum protein concentration when the protein content of the diet is limited. Hence it is not to be expected that the choline esterase value should fall during brief inanition. Nor is any such drop observed in experiments on changes in diet, as shown by Milhorat.

It is thus possible on the basis of our knowledge regarding the



formation of the serum albumin to give a rather exhaustive analysis of the conditions which we find in case of the serum choline esterase, and especially of the variations shown by the serum choline esterase in the single individual as well as from one individual to the other.

### Summary.

It was shown in a previous paper that low values for the serum choline esterase are found in a number of diseases which have in common that the serum albumin likewise is low. This observation, which is supported by the fact that the choline esterase in fractionation tests with ammonium sulphate is precipitated along with the albumin fraction, is made the object of further investigation. It is demonstrated that in serum we find a simple correlation between these two substances, a correlation which is observed on examination of several patients as well as on examination of patients whose serum albumin concentration varies. The cause of this correlation is discussed. The most plausible explanation seems to be that albumin and choline esterase both are secreted into the serum from the same cells, and presumably in a fairly constant ratio. Since everything indicates that the serum albumin is formed in the liver, it follows that this organ must also be the origin for the serum choline esterase. It is shown that the protein content of the diet, which may produce variations in the serum albumin, also will cause corresponding changes in the serum choline esterase concentration.

### Litterature.

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## Experience with intravenous heparin treatment by the veinseeker in the treatment and preven- tion of thrombosis and in treating endocarditis *lenta*.

By

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(Submitted for publication January 15, 1943.)

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It seems unnecessary, in these Acta, to dwell upon the significance, the application and prospective possibilities of heparin in the combat of thrombosis, as Scandinavian workers, especially, have so much contributed to the isolation and the study of this substance [Jorpes, Crafoord, etc. (1. 2. 3. 4. 5. 6. 7. 9. 10. 16. 25. 26. 27. 28. 29.)]. On the method of administration and the dosage, opinions are still divergent.

### *Method of administration.*

Practically all of the Scandinavian authors carry out heparinization by means of 4 intravenous injections pro die. Their results, in general, are excellent, but Crafoord (5) and Hedenius (6) also saw failures, i.e. the development of thrombosis in spite of giving heparin. The latter, probably rightly, ascribed this to insufficient dosage.

Gordon Murray (20. 21. 22. 23. 24), as well as the other Canadian and American workers (11. 18. 19), applies permanent hepariniza-

tion by means of intravenous drip infusion, by which the patient's clotting-time is maintained day and night at 15—20 minutes. In his very large series no failures occur (24).

The drawbacks of drip infusion, however, have withheld many people from the use of heparin, and we think to have succeeded in overcoming these difficulties in the following way.

The »veinseeker» (see fig. 1), described by Ronald Edwards, is filled with a heparin solution and normal saline, the air being expelled by swinging. The vein is then punctured, with the rubber teat or tube just a little compressed. As soon as one has arrived within the vein, the blood becomes visible in the sight-glass.

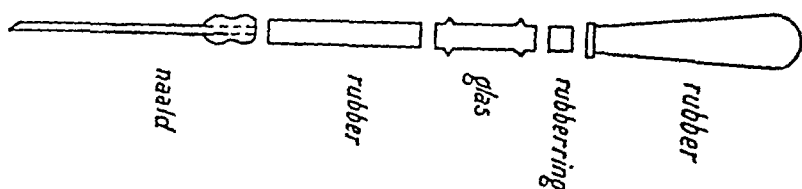


Fig. 1. Ronald Edwards's »veinseeker».

(*British Medical Journal*, 957, 1939).

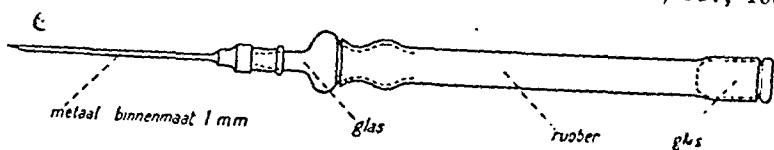


Fig. 2. Veinseeker; new modification with glass nozzle.

The veinseeker is then fastened to the arm with adhesive plaster. Heparin can now be injected every hour by a nurse into the rubber tube, after cleansing the latter with ether or alcohol. The heparin prevents clotting in the needle that lies in the vein, provided the latter is not too narrow. We successfully used a stainless needle 40 mm long, with a bore of 1 mm, polished inside. The injection pricks in the rubber tube immediately close by themselves after the needle is withdrawn.

Fig. 2 shows a modification of the veinseeker, which we (12, 13) have, as yet, only used in one patient. By the nozzle carrying the needle being of glass, the sight glass can be left out. We found the rubber teat also to be unnecessary.

One should preferably choose a vein on the fore-arm, as this allows the arm to move freely in the elbow-joint. But even if a cubital vein is used, no splinting is required. We tie the arm to

the bed or pillow by a very loose strap, as to remind the patient not to take too much movement, smaller movements being permitted. In our experience, the needle has never perforated the wall of the vein. Thus in the majority of cases it will not be necessary to make use of a special needle, a needle with bulb-stilette [W. J. Kolff (14)] a small troicart, or to introduce a rubber tube into the vein. It is neither necessary to expose the vein by dissection. The arm must not lie too low, as this would cause leakage along the needle.

We recently learned that Olovson has already designed a needle based on the same principle [Rosenquist (26)]. The sight glass in the veinseeker appears to me to be an advantage.

#### *Personal experience with heparin treatment.*

We have treated six patients with heparin (13). We started with intravenous drip infusions, then tried multiple intravenous injections, and finally arrived at the use of the veinseeker. Five patients have been treated with this instrument, for periods of 12 hours, 4 days, 4 days, 6 days and 8 days respectively.

At post-mortem examination of a patient, who had retained the needle in his arm for 6 days, the vein was found completely intact, without any trace of thrombosis, the usefulness of the veinseeker being thus established.

Only two patients have recovered: one puerpera, who had thrombosis of her left leg with pulmonary embolism, who would have had a good chance of recovery even without heparin; and one patient suspect of thrombosis of the cavernous sinus. None of the others belonged to the group of post-operative thrombosis, in which heparin treatment has its best prospects, but could all be considered beforehand as lost cases: one with inveterate thrombosis of the central vein of the retina, one with thrombosis of the cavernous sinus, two with endocarditis lenta, one with septic thrombosis of the jugular vein. We had, however, the opportunity of gathering some valuable evidence during the treatment.

#### *Undesirable reactions after heparin.*

The preparation used in recent times was a heparin concentrate Promonta (»trombo-vetren«)<sup>1</sup>, which was tolerated by the

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<sup>1</sup> The heparin was placed at our disposition by the Promonta Chemical Works.

patients without any disagreeable reaction. With an earlier preparation we had anaphylactoid reactions with fever, just as have been described by others with the use of the older preparations. At present reactions are no more to be feared.

### *Haemorrhage round embolic foci.*

There is very little fear of embolism after heparinization of patients with the common type of post-operative thrombosis. It is hardly ever met with, and then only during the first hours of treatment. This is easily understood, as heparin does not dissolve or attack an existing thrombus, but only prevents its further growth and embolism is exactly caused by the freshly accreted parts of thrombi.

Things are otherwise, however, in endocarditis lenta. In an editorial article of the J. A. M. A. (176, 25, 1646, 1941) four fatal embolisms are described during heparin treatment of endocarditis lenta. Kelson and White (11) advise not to start heparin treatment till the blood-cultures have been rendered negative by chemotherapy; but one of our patients with sepsis lenta died, after 8 days' treatment, of a large haemorrhage round a cerebral embolus, confirmed at autopsy, although the temperature had become normal and the blood-culture negative. Nevertheless it is justified to try heparin combined with chemotherapy in these patients in view of the results claimed by Lichtman and Bierman (11.5 per cent recovery). (17).

In a young adult with thrombosis of the cavernous sinus and staphylococcal sepsis, who shown at first distinct improvement of the local process, post mortem numerous large haemorrhages were found round pulmonary emboli. Round fresh emboli, therefore, severe haemorrhages actually may occur, at least in a patient with septic thrombophlebitis.

### *Heparin and infection.*

In the treatment of septic thrombosis and endocarditis lenta with the combination of heparin with a chemotherapeutic, the accretion of the thrombus can be prevented by the heparin, but eventual success can only be expected when the chemotherapeutic is able to attack the causative organism.

One must, however, be aware of the possibility of heparin influencing the defence mechanism of the body unfavorably. It is a known fact, for instance, that heparin in high dilution links up with equal avidity with complement as with thrombin [Jorpes (9)]. (Another substance inhibiting blood-clotting, liquoid Roche, even completely annihilates the bactericidal action of blood). Meyer, Friedman, Hamburger and Katz (19) observed acute glomerulonephritis in a patient with endocarditis lenta, treated by them with heparin without chemotherapy. They ascribe this accident to the flow of organism suddenly released from the thrombus.

### *Dosage. Latent heparinization.*

We were struck by the fact that the amount of heparin required for lengthening the clotting-time<sup>1</sup> to over 15 minutes, is much smaller in the patients with sepsis lenta (fig. 3 and 4) than in the other patients. Perhaps this results from less extensive thrombosis and less pyrexia.<sup>2</sup> In a patient with sepsis lenta 25 mg of heparin an hour were sufficient to keep the clotting-time permanently lengthened. In patients with septic thrombosis over 100 mg. an hour were required (fig. 5 and 6). Very probably the most economic way of administration is the drip infusion. With the veinseeker, the more frequent the injections, the smaller will be the required amount. We finally arrived at hourly doses.

The injected heparin is partly eliminated by the urin [which is confused by Jacques (7 a)], partly linked up or otherwise inactivated. A few hours after an injection of heparin the clotting-time is normal again.

After repeated injections the organism shows a certain wearing off of the capacity of linking up heparin. Jores and Detzel (8) could show this very distinctly in dogs and cats (fig. 7).

Crafoord (5) had already observed, that after an operation more heparin was required than before, which is ascribed to the thrombin

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<sup>1</sup> The clotting-time was determined with a capillary tube, the blood being withdrawn from a prick in the finger. A too narrow tube and too small prick can result in a too short time-reading. A number of control estimations made with a wider tube showed fair agreement.

<sup>2</sup> One must keep in mind that heparin is very difficult to standardize, and that the activity is not always proportional to weight (personal communication of «Promonta»).

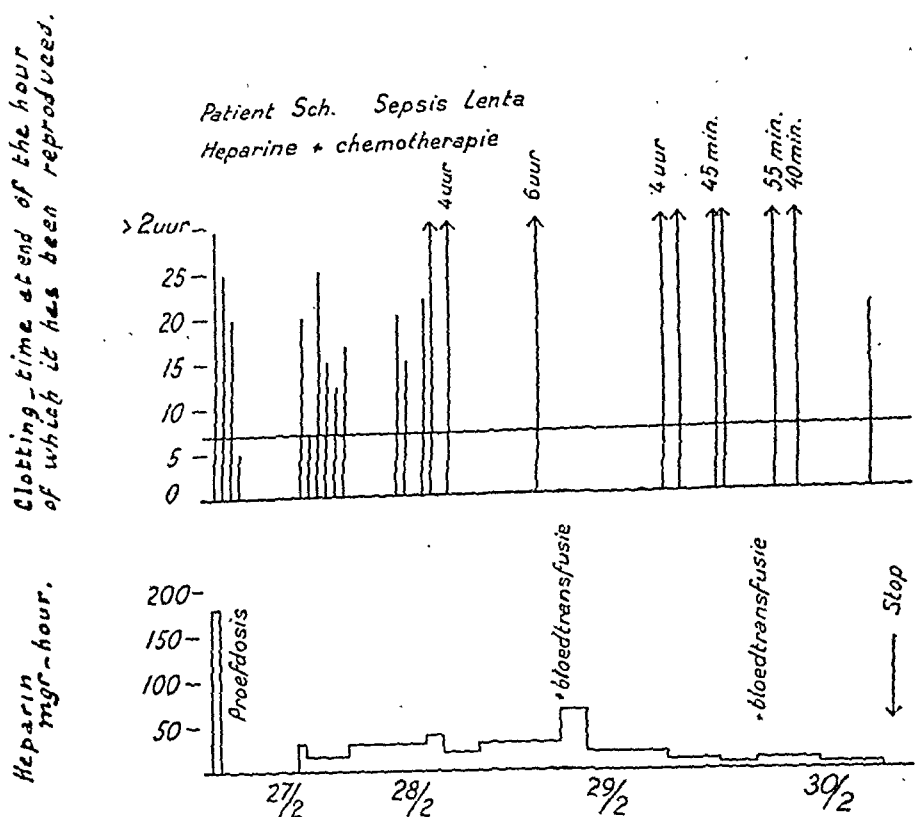


Fig 3 and 4. Two patients with sepsis lenta, both treated with heparin and chemotherapy. Fig. 3 with drip infusion, fig. 4 with veinseeker. The clotting-times are plotted out as vertical lines, or as arrows when the times exceed 25 minutes. The amount of heparin injected in the corresponding hour is found vertically below.

formed in the operation area. Personally we saw in non-operative patients, that at the onset of treatment more heparin is necessary to lengthen the clotting-time than some time later (fig. 3 and 4). Fig. 5 also suggests a smaller amount to be required once the patient is heparinized. This is of practical importance. In order to get the patient duly heparinized, one must start with large doses and continue with smaller ones. Thus a condition of »latent heparinization» can be created, in which the clotting-time is normal or slightly raised, but can be markedly lengthened by an additional small dose, that would be otherwise inactive.

In the future I intend to proceed, by way of experiment, in such a way, that the patient is brought mainly in a state of latent heparinization, so that, after a higher initial dose, so little heparin is hourly injected, that 10 minutes after each injection the clotting-



Heparin mgr.-hour.

Clotting-time at end of the hour of which it has been reproduced.

Patient R.W. Sepsis Lenta (Heparine + Chemotherapie)

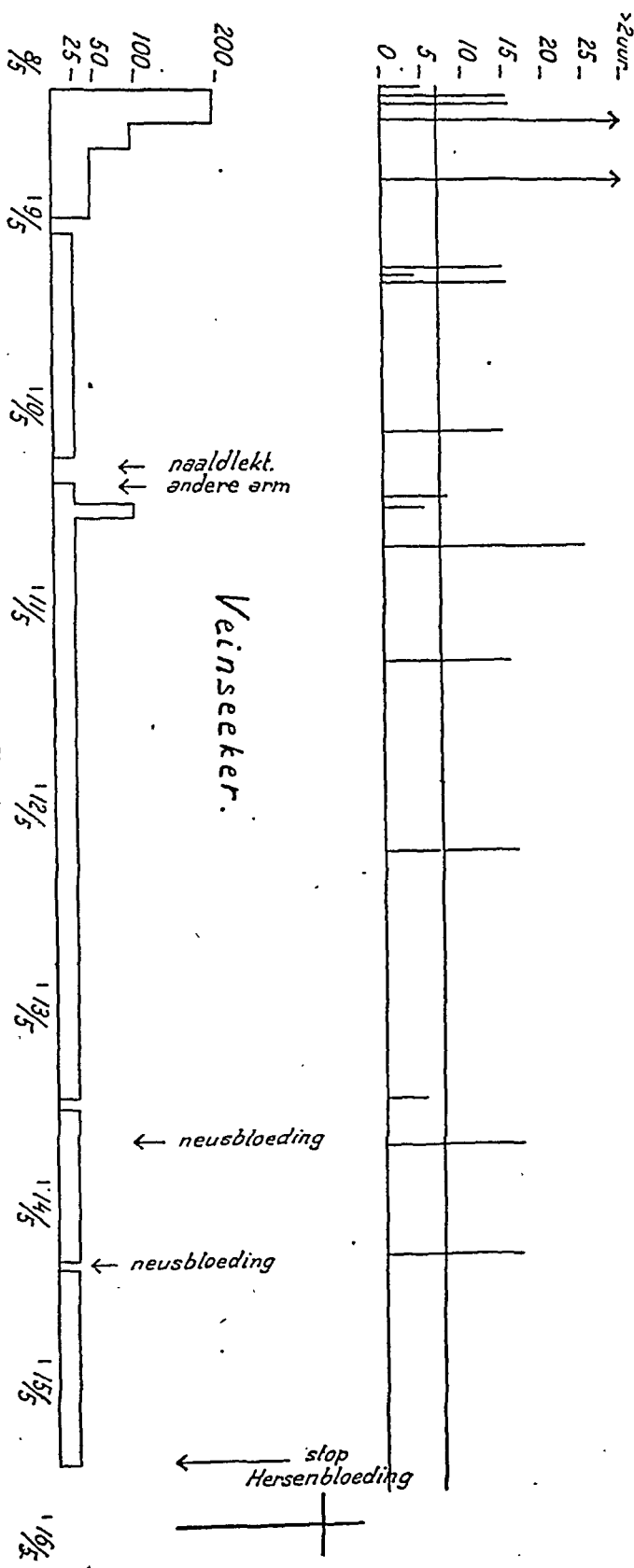


Fig. 4.

Heparin mgr.-hour. Clotting-time at end of the hour of which it has been reproduced.

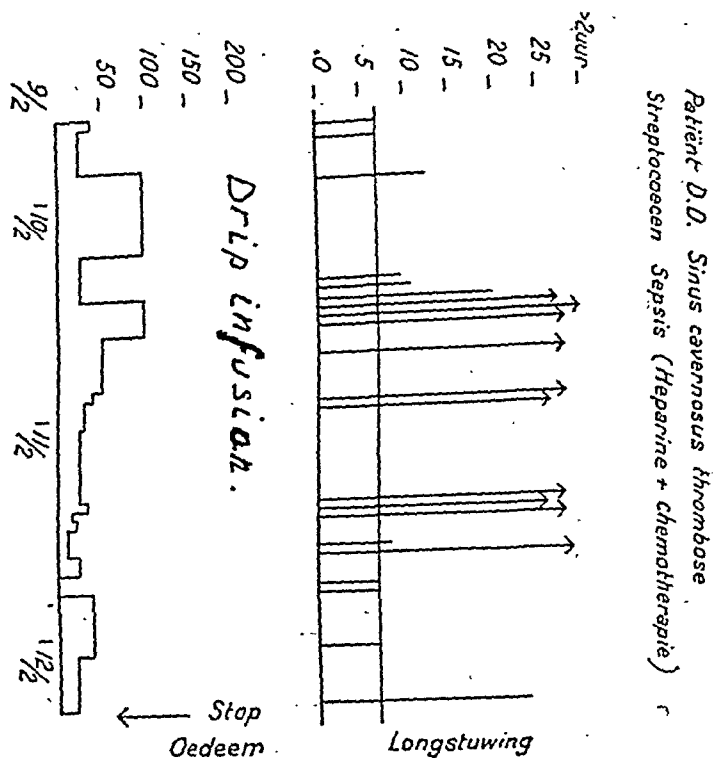
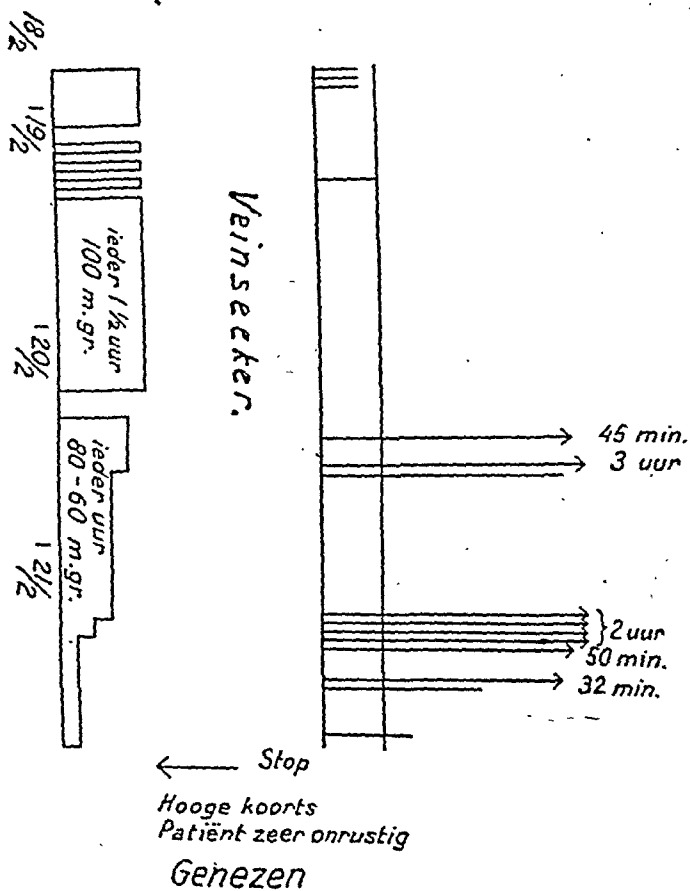


Fig. 5.



Heparin mgr-hr

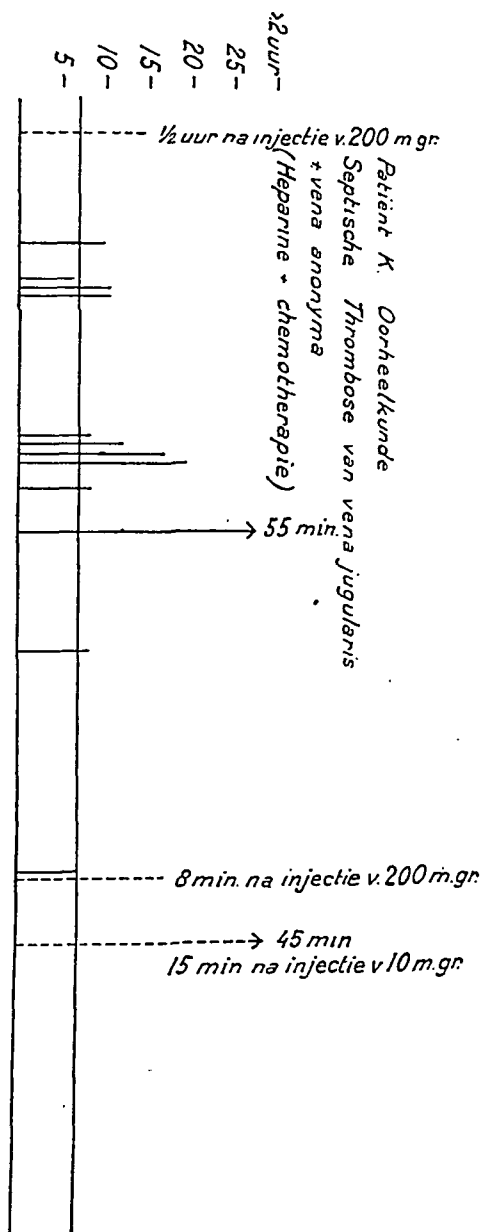
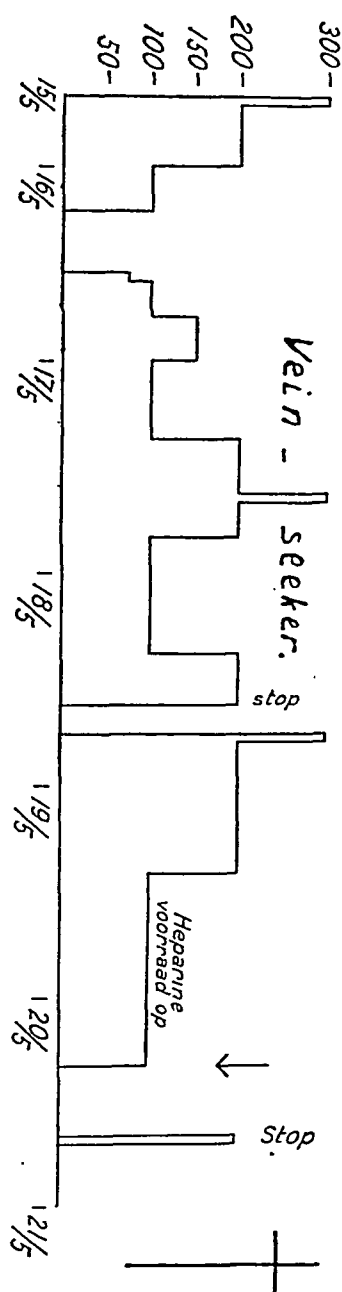
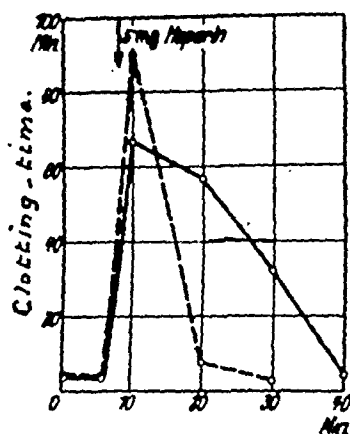
Clotting-time at end of the hour  
of which it has been reproduced.

Fig. 6.

time is just perceptibly lengthened. The excess of thrombin round the thrombus can thus be continually neutralized.



Jores en Detzel

Fig. 7. Effect of 5 mg of heparin intravenously on a dog, weighing 10 kg, in pernocton anaesthesia. Between experiment 1. (-----) and 2. (——) 40 mg of heparin were given intravenously.

### Dosage scheme for heparin.

#### Scandinavian dosage.

4 intravenous injections a day, namely 3 of 50 mg and at night one of 100 mg for some 10 days.

#### American dosage.

Heparin by intravenous drip infusion, to be regulated as to keep the clotting-time permanently at 15—20 minutes. This requires about 10—20 mg heparin an hour, more at the onset. Duration: 4—6 days or more.

#### Dosage by »weinseeker».

All injections are given into the rubber tube. Injections every hour, starting with 200 mg, later 100, 50 and finally 10 mg every hour. Control of the clotting-time, the dosage being probably sufficient when this is still lengthened 10 minutes after each injection. In the surgery of the vascular system higher doses are desirable, so that the clotting-time is still lengthened at the end of the hour. Duration 6 days or longer.

### Summary.

By the use of the *veinseeker* it is possible to apply intravenous heparin administration very frequently without drip-infusion or repeated intravenous injections.

In heparinized patients with sepsis lenta and septic thrombophlebitis, large haemorrhages around emboli can occur.

It is found that, in non-operated patients too, after some time less heparin is required for lengthening the clotting-time, than at the onset of treatment. A condition of latent heparinization can exist. The author will try in the future to keep on the borderline of this latent heparinization, with slight lengthening of the clotting-time, in the treatment, and especially the prophylaxis of thrombosis.

### Post-Scriptum.

Since I sent this article to the press for the first time one year ago I can add the following experiences. Four more patients were treated with heparin by the *veinseeker* method and kept on the borderline of latent heparinization and a slight lengthening of the clotting-time. In two patients we were obligated to stop the treatment owing to chills due to heparin. In one patient a tuberculous gravide with established thrombosis in one leg and beginning thrombosis of the other leg the success was evident. In other investigations we sometimes found the so called *negative phase* i. e. a shortening of the clotting-time, 5 to 13 hours after a heparine injection. As the existence of a negative phase which would be of great importance is generally denied in literature investigations on this subject are going on.

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## Investigations on the Passage of Sulfathiazole through the Blood-Liquor Barrier in various Forms of Meningitis.

By

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After the introduction of sulfonamides in the treatment of meningitis the question as to the ability of medicaments to penetrate from the blood into the cerebrospinal fluid has gained renewed interest. As far as the sulfonamides are concerned it appears that the ability to penetrate into the cerebrospinal fluid varies greatly with each individual sulfonamide derivate.

While sulfanilamide is present in almost the same concentration in the cerebrospinal fluid and the blood (Katzenelbogen, Cruvant, and Silverberg, 1941), the ratio between the concentration in the cerebrospinal fluid and in the blood, the liquor-blood quotient (L. B. Q.) is c. 0.70 for sulfapyridine (Roelsen and Simesen, 1941, Engbæk, Nissen and Schleisner, 1941, Bechgaard, Lohse and Vermehren, 1941) and about 0.20 for Sulfathiazole (*idem*). These figures, however, only apply to cases in which the meninges are intact. In certain forms of meningitis, especially purulent and tubercular meningitis, considerably larger amounts of sulfapyridine and especially of sulfathiazole pass into the cerebrospinal fluid, so that the L. B. Q. increases.

This fact is partly of therapeutic partly of diagnostic interest. The therapeutic significance of the increased L. B. Q. has been dealt with by several authors, especially by Roelsen and Simesen, (1941), Engbæk, Nissen and Schleisner (1941), and Bechgaard, Lohse and Vermehren (1941) and will not be further discussed here. On the other hand, the significance of the L. B. Q. for the diagnosis of the various forms of meningitis has merely been suggested by Roelsen and Simesen (1941), who think that in the L. B. Q. there may be a means of distinguishing by differential diagnosis between a tubercular and a serous meningitis — a distinction which may often cause clinical difficulties and which is of considerable importance in view of the prognosis to be communicated to the relatives of the patient.

The object of this work has in the main been to try to verify this conjecture. In connection with the present series of investigations the L. B. Q. in a number of other forms of meningitis has been determined, just as the normal L. B. Q. has been determined by the examination of a number of patients without meningeal changes.

Before we give an account of the results of the investigations some few words must be said about the nature of the blood-liquor barrier.

The demonstration of the existence of a barrier between the blood and the cerebrospinal fluid is due to Ehrlich (1885) and Goldmann (1912) who by the injection of a series of stains showed that only a small number of the stains were able to penetrate to the fluid.

The barrier is generally stated to be situated in the capillary net in the leptomeninges, especially in the choroid plexus.

It must, however, be pointed out that there undoubtedly exists yet another barrier, namely the blood-brain barrier.

The mechanism of the passage of the various substances through the blood-liquor barrier is not yet fully cleared up, and a detailed discussion of it would take us too far afield. The problems have been thoroughly treated, for instance in the papers by Walther (1929), Kafka (1930) and Bromann (1938).

We shall merely point out that in many respects the spinal fluid has the character of an ultrafiltrate or a dialysate. This is suggested in the first place by the low content of colloids in the fluid.



If the spinal fluid were to be conceived as a simple ultrafiltrate or a dialysate it must, however, be expected that all crystalloids would be distributed approximately equally on either side of the membrane, if the solubility of the substances in the two phases, the adsorption of the substances to the protein molecules in the blood, and the Donnan equilibrium are taken into account.

While ions as  $\text{Ca}^{++}$ ,  $\text{Na}^+$ , and  $\text{Cl}^-$  approximately satisfy these requirements, there are such far-reaching discrepancies between the distribution of such ions as  $\text{Mg}^{++}$ ,  $\text{K}^-$ , and  $\text{PO}_4^{--}$  and of the anelectrolyte glucose in the blood and the spinal fluid that the theory of the formation of the fluid on the basis of simple physicochemical processes cannot be maintained. It is a fact, however, that the ratio between the distribution of the individual substances in the fluid and in the blood (the Liquor-Blood Quotient lies within) rather narrow limits as long as the barrier is intact.

Of the foreign substances introduced into the organism some will not be able to force the barrier at all.

That, for instance, is the case with salvarsan (Stühmer 1915 and others) and basic stains (Wittgenstein and Krebs, 1926).

Of others only a certain percentage can pass into the spinal fluid.

But if the barrier is injured, the constant distribution of the substances on the two sides cannot be maintained, and in the change in the quotient we have a certain measure of the lesion to the barrier. This applies to the normal as well as to the foreign substances. It is pointed out by several authors, however, that the change in the quotient is not a direct measure of the extent of the lesion.

The lesion changing the degree of permeability may partly be of an inflammatory, partly of a traumatic kind, just as certain medicaments are able to alter the permeability. Thus, after the ingestion of theophyllin, histamine, and adrenaline there is an increase in the permeability (L. Stern, 1923).

As was only to be expected, it has been attempted, by investigation of the permeability for various substances both normal to and foreign to the body, to find a test that might express the extent of the injury to the barrier (meninges).

Especially in the years 1920—30 a fairly extensive literature was published on the value of various permeability tests, the most

The day before the test was performed the sulfonamide derivate in question was administered in the following doses:

Adults and children over 15 years old .....	1 g $\times$ 6
Children from 10 to 15 years old .....	$\frac{3}{4}$ g $\times$ 6
Children from 1 $\frac{1}{4}$ to 10 years old .....	$\frac{1}{2}$ g $\times$ 6
Children under 1 $\frac{1}{2}$ years old .....	$\frac{1}{4}$ g $\times$ 6

This dosage, however, was only kept up in cases in which the sulfonamide derivate was given exclusively for diagnostic purposes. In cases in which the substance was also given for therapeutic reasons the doses were in most cases somewhat larger, as will appear from the table overleaf.

After the substance had been administered throughout one day, lumbar puncture and venous puncture were performed simultaneously 2 hours after the ingestion of a dose. Liquoid Roche was added to the blood as an anticoagulate. Part of the cerebrospinal fluid was kept for the counting of the cells and protein determination. With the rest of the cerebrospinal fluid (1  $\frac{1}{2}$ —2 cm<sup>3</sup>) and with the blood (2—4 cm<sup>3</sup>) the sulfonamide content was determined according to the method of Hecht (1938).

Since it is normally only the free, that is to say, the non-acetylated, compound of the sulfonamide derivate that passes into the cerebrospinal fluid, the L. B. Q. is exclusively determined by division of the concentration of free compound in the cerebrospinal fluid by the free compound in the blood.

The investigation comprises determinations of the L. B. Q. partly in persons with a normal cerebrospinal fluid, partly in patients admitted to the Blegdamshospital suffering from various meningeal affections.

We will first describe

### *A. The normal Material*

comprising determinations of

1) The L. B. Q. for sulphathiazole in 9 adults and 11 children with non-meningeal affections.

2) The L. B. Q. for sulphapyridine in 10 children with non-meningeal affections.

The persons chosen for the experiments were patients with

Table I.

The Spinal Fluid-Blood Quotient for Normal Persons after Ingestion of Sulfathiazole.

No.	Age	Diagnosis	Concentration in mg %				Quotient	
			in spinal fluid		in blood		free	total
			free	total	free	total		
Children								
1	5	Measles	0.86	0.86	4.9	6.8	0.17	0.13
2	7	»	0.60		4.2	5.1	0.14	
3	1 ½	»	0.88		4.5	7.0	0.19	
4	2	»	0.48		2.6	4.0	0.18	
5		»	0.63	0.64	4.9	6.0	0.13	
6	3 ½	»	0.38	0.41	3.2	4.6	0.12	
7	1	»	0.57	0.57	3.1	4.4	0.18	
8	7 ½	»	0.97	0.97	4.4	6.4	0.22	
9	6¾	»	0.75	0.76	4.5	5.5	0.17	
10	5	»	0.9	1.1	5.8	6.2	0.16	
11	7	»	0.66	0.66	4.6	5.9	0.14	
Adults.								
1	17	Measles	0.40	0.50	3.3	4.7	0.12	0.11
2	33	Chicken-pox	0.7	0.9	3.1	5.4	0.22	
3	20	Bacilluscarrier	0.5	0.5	2.5	4.5	0.20	
4	21	»	0.38		2.5	3.1	0.15	
5	15	Mumps	0.8	0.8	4.6	5.0	0.17	
6	30	unspecif. eczema	0.55	1.6	4.1	5.8	0.12	
7	17	Syphilis	0.4	0.4	2.4	2.7	0.17	
8	23	Syphilis	1.3	1.3	5.8	6.3	0.22	
9	21	Gonorrhoea	0.6	0.6	3.3	3.7	0.18	

mild cases of infectious diseases, predominantly measles, or entirely normal persons all with normal findings in the cerebrospinal fluid.

The results will appear from Tables I and II.

It will be seen from Table I that after the ingestion of sulfathiazole the L. B. Q. is fairly constant, ranging from 0.12 to 0.22, and with a mean value of 0.17. The quotient is the same for adults and children. As regards the absolute concentrations obtained, the concentration for the free compound in the blood lies between 5.8 and 2.5 mg % with a mean value of 3.92, while for the free compound in the spinal fluid it ranges from 1.3 to 0.38 mg % with an average value of 0.67.

Table II.

The Spinal Fluid-Blood Quotient in Normal Children after Ingestion of Sulfapyridine.

No.	Age	Diagnosis	Concentration in mg %.				Quotient	
			in spin. fluid		in blood		free	total
			free	total	free	total		
1	6 <sup>3</sup> / <sub>4</sub>	Measles	4.3	4.3	5.2	8.1	0.83	0.53
2	3	"	2.4	3.1	3.9	7.8	0.62	
3	3	"	4.6	4.7	7.0	8.9	0.66	0.53
4	3	"	2.1	2.5	2.7	5.3	0.78	
5	6	"	4.2		5.0	6.9	0.84	
6	10/12	Tussis conv.						
		Pneumonia	16.6	17.4	28.5	36.0	0.59	0.48
7	6	Mumps	1.5		2.7	5.6	0.55	
8	9	"	2.0	2.1	3.3	5.4	0.61	0.38
9	9	"	3.9	4.0	5.7	6.7	0.68	0.60
10	17	"	3.6	3.6	5.1		0.71	

The amount of the quotient after ingestion of sulfapyridine will appear from Table II.

It will be seen that after ingestion of sulphapyridine the L. B. Q. lies considerably higher than after ingestion of sulfathiazole. The mean value is 0.69, varying between 0.55 and 0.83. The absolute values for the free compound in the blood lie between 28.5 and 2.7 mg % with a mean value of 6.91 mg % and for the free compound in the spinal fluid between 16.6 and 1.5 mg % with a mean value of 4.52 mg %.

The great amplitude of variation within the normal makes sulfapyridine unsuitable for the functional test.

Therefore only sulfathiazole has been used for the investigations on the permeability of the blood-spinal fluid barrier in patients with meningeal affections.

#### B. The Material of the L. B. Q. in Patients suffering from meningeal Affections.

comprises the following determinations.

1) The L. B. Q. in patients suffering from tubercular meningitis.

2) The L. B. Q. in patients suffering from secondary lymphocytic meningitis.

3) The L. B. Q. in patients suffering from primary lymphocytic meningitis.

4) The L. B. Q. in patients with purulent meningitis, examined immediately after admission.

5) The L. B. Q. in patients suffering from purulent meningitis under observation for some time, and

6) The L. B. Q. in patients suffering from infectious diseases of the central nervous system of a kind other than those already mentioned.

The investigations of the size of the L. B. Q. in patients suffering from tubercular meningitis will appear from Table III.

As will be seen in the table, in all the cases examined the quotient had risen essentially. The values range from 0.32 to 0.55, the mean value being 0.42.

Thus it would seem that a considerable change in the permeability of the meninges with a much increased passage of sulphathiazole to the spinal fluid is one of the features of Meningitis tuberculosa.

As will appear from the table most of the investigations were made at rather a late stage of the disease, in some few cases even a short time before death. In 2 cases, however, (Nos. 2 and 6) the first investigation was made a fortnight before of death.

The column headed Degree affected shows the condition of the patient at the time the test was made. The patient's condition is denoted by I, II, or III, where I means not or lightly affected, without neurological changes, II moderately effected, with clouded senses and/or lighter neurological changes, while III denotes greatly affected, i. e. with clouded perception, comatose, and/or with massive neurological changes.

No distinct parallelism between the gravity of the disease and the size of the quotient appears from the table.

How early in the picture of the disease the quotient increases cannot be said with certainty.

It is seen, however, that in several cases the quotient is increased at a time when the clinical conditions is not much affected (Nos. 2 and 5).

It is further seen that in the 4 cases which have been under

Table  
Spinal Fluid-Blood Quotient in

No.	Age	Admitted	Date	Lumbar Puncture				Degree affected	Dose
				Cells		Alb.	Glob.		
				Numbers	Kind				
1	23	20/5	28/5	374/3	50 % mono	40	4	III	g 1×6
2	25	15/6	19/6	537/3	m	30	4	I	g 1×6
3	29	6/10	8/10	733/3	m	8	4	III	g 1×6
4	32	7/1	8/1	76/3	m	not determined		II	g 1.5×6
			9/1	816/3	m	50	7	II	?
			10/1	264/3	m	50	8	III	?
5	20	9/2	10/2	416/3	m	40	6	I	g 1.5×6
			12/2	81/3	m	40	6	I	g 1×6
6	25	14/2	25/2	480/3	m	30	3	II	g 1×6
			27/2	128/3	m	30	4	III	
7	10	23/2	1/3					III	
			25/2	420/3	m	50	4	II	g ¾×6
			27/3	312/3	m	too little	1	II	g ¾×6
8	2	17/4	21/4	203/3	80 % m	100	10	III	g ½×6
9	25	5/5	9/5	not determined				III	g 1×6
10	7	9/4	22/4	92/3	m	20	1	III	g ¾×6

observation for some time during which the patient was gradually getting worse the quotient is increasing, except in one case (No. 6).

Conditions in the cases of non-tubercular lymphocytic meningitis will appear from Table IV.

This table shows instances of the so-called secondary lymphocytic meningitis, i. e. meningitis in conjunction with some infectious disease, in the majority of cases mumps.

From this table it appears that in all cases examined the quotient lies between 0.14 and 0.23 with a mean value of 0.18. In other

## III.

*Patients with Tubercular Meningitis.*

Sulfathiazole Conc. in mg %				Quo- tient	Died	Comments
in spin. fl.		in blood				
free	total	free	total			
1.2	1.2	3.0	3.9	0.40	29/5	Sect.: Meningitis tub. Tumor ovarii.
0.94	1.0	2.6	4.1	0.36	3/7	Sect.: Tub. miliaris. Meningitis tub. Tub. pulm. bilat.
1.4		3.4	4.0	0.41	12/10	Sect.: Tub. miliaris. hepat. et ren. Meningitis tub. Tub. cavern. pulm.
1.2	1.5	2.6	3.6	0.46	10/1	Sect.: Meningitis tub. Tub. mili- aris pulm. et ren.
1.3	1.6	2.5	3.6	0.52		
2.1	2.6	3.9	5.3	0.54		
0.8	0.9	2.5	3.4	0.32	27/2	Sect.: Meningitis tub. Tub. mili- aris pulm. et ren. et hepat.
1.1	1.5	2.7	3.8	0.41		
0.6	0.7	1.7	2.4	0.35	9/3	Sect.: Meningitis tub. Tub. mili- aris.
2.5	2.9	4.5	6.4	0.55		
0.4	0.6	1.3	1.8	0.31		
1.5	1.6	4.0	4.8	0.38	5/3	Sect.: Meningitis tub.
2.1	2.4	4.3	4.5	0.49		
3.2	3.6	7.7	8.8	0.37	22/4	Sect.: Meningitis tub. Tub. mili- aris.
1.15	1.35	2.42	2.65	0.47	13/5	Sect.: Meningitis tub. Broncho- pneumonia. lob. inf. sin.
1.9	2.1	5.1	5.7	0.37	23/4	No section.

words, it is at exactly the same level as in normal persons (Table I).

Conditions are slightly different in the group termed primary lymphocytic meningitis entered in Table V. The table shows the result of the first examination of the spinal fluid after admission as well as the spinal fluid findings simultaneously with the determination of the quotient. In 4 cases the quotient was determined over a prolonged period during the course of the disease.

It is seen that in the majority of cases the quotient is normal,

Table IV.  
Spinal Fluid-Blood Quotient in Patients with Secondary Lymphocytic Meningitis.

No.	Age	Diagnosis	Ad- mit- ted	Date	Lumbar puncture			Degree affect- ed	Conc. of Sulfathiazole in mg %				Quo- tient	
					Cells		Alb.		Glob.	in sp. fl.		in blood		
					Num- bers	Kind				free	total	free		total
1	21	Tonsillitis ac. Enteritis ac. Meningitis lymph. sec.	14/9	23/9	23/3	m.	10	0	I	0.5	0.5	3.5	3.6	0.14
2	13	Tonsillitis ac. Enteritis ac.	30/9	7/10	12/3	m.	10	0	I	0.6	0.6	3.6	4.5	0.16
3	10	Meningitis lymph. sec. Parotitidis seqv. Meningo-encephal.	3/10	7/10	174/3	m.	10	0	I	0.6		3.7	4.6	0.17
4	4	Parotitis epid.	16/10	22/10	1184/3	m.	10	1	I	0.9	1.0	6.1	8.0	0.15
5	27	Meningitis lymph. sec. Parotitis epid.	4/11	6/11	976/3	m.	10	too little	I	1.0	1.0	5.1	6.7	0.19
6	32	Meningitis lymph. sec. Parotitis epid. Otitis media. Syphilis cong.	4/11	6/11	152/3	m.	20	0	I	0.9	1.0	4.2	5.7	0.22
7	17	Meningitis lymph. sec. Parotitis epid.	29/11	1/12	1068/3	m.	30	0	I	1.1	1.1	4.7	5.8	0.23
8	7	Meningitis lymph. sec. Parotitis epid.	25/11	1/12	6/3	m.	10	0	I	0.7	0.7	3.3	4.5	0.21
9	10	Meningitis lymph. sec. Parotitis epid. Meningitis lymph. sec.	25/01	29/11	799/5	m.	20	0	I	0.4	0.4	2.7	3.2	0.15



Table  
*Spinal Fluid-Blood Quotient in*

No.	Age	Condition at determ. of quotient	Lumbar puncture at determ. of quotient				No. of days between admittan- ce and det. of quot.	Dose
			Cells		Alb.	Glob.		
			Numbers	Kind				
1	60	I	3500/3	50 % poly	30	0	2	g 1×8
2	8	II	10400/3	poly	40	2	4	g 1×6
3	22	II	1236/3	poly	30	3	2	g 1×8
4	21	III	2250/3	poly	50	4	2	g 1.5×6
5	12	I	3000/3	poly	30	3	2	g 1×6
6	2	I	10000/3	poly	20	2	1	g 0.5×8
7	14	I	500/3	50 % poly	20	0	3	g 1×6
8	21	I	130/3	mono.	10	1	3	g 1×6
9	21	III	26600/3	poly	200	20	1	g 1×8
10	21	I	134/3	mono.	10	0	6	g 1×6
11	20	I	80000/3	poly	30	0	2	g 1.5×6
12	36	III	100000/3	poly	90	0	1	g 1.5×6
13	27	II	34/3	50 % poly	40	1	1	g 1×8
14	29	I—II	2016/3	poly	40	2	2	g 1×8
15	18	II	20800/3	poly	100	9	1	g 1×6
16	28	I	680/3	75 % poly	20	0	1	g 1×8
17	29		1670/3	poly	10	0	1	g 1×6
18	3	II	5280/3	poly	40	2	4	g 1×6
19	23	I	3200/3	poly	40	4	1	g 1×6

On the other hand, in the remaining two patients with a quotient exceeding the normal range the course of the disease clinically differs so much from what is usually seen that a brief report of the case history may be of interest.

The patient (No. 7) had suddenly been taken ill two days before admission with shivering fits and general malaise. The next few days he became increasingly somnolent and upon admission was

## VI.

*Patients with Purulent Meningitis.*

Conc. of Sulphathiazole in mg %				Quot.	Comments
in sp. fluid		in blood			
free	total	free	total		
1.2	1.3	4.3	5.8	0.28	Bact. not found.
0.6	0.6	2.3	2.9	0.26	Bact. not found.
1.0	1.0	2.7	3.5	0.37	Bact. not found.
2.2	2.4	4.3	7.1	0.51	Growth of Meningoc. Paresis of the ab- cens nerve. Total deafness.
2.0		5.0	6.0	0.40	Growth of Streptoc.
1.4	1.5	9.4	12.0	0.15	Growth of Meningoc.
0.8	0.9	2.9	5.5	0.26	Growth of Meningoc.
1.1	1.1	3.2	4.6	0.34	Bact. not found.
1.9	2.2	5.0	6.8	0.38	Growth of Meningoc. Very ill, Paresis of the facial nerve.
0.6	0.6	1.7	3.0	0.35	Growth of Meningoc.
1.9	2.2	9.1	9.8	0.21	Bact. not found.
3.0		7.2	10.7	0.42	Growth of Meningoc.
1.9	1.9	4.7	6.0	0.41	Growth of Meningoc.
1.3	1.5	3.9	4.7	0.33	Bact. not found.
1.6	1.8	5.1	6.2	0.31	
2.1		6.4	9.5	0.33	Growth of Meningoc.
1.0	1.0	3.4	3.5	0.29	
1.6		5.0	6.4	0.32	Growth of B. Pfeiffer. Died on 30th day after det. of Quot.
1.5	1.6	5.1	6.7	0.29	Growth of Pneumoc.

remote, with clouded perceptions and almost comatose. In the course of the next day he cleared up, however, and apart from the spinal fluid test all other examinations showed normal conditions.

Patient No. 9 had been taken ill two days before admission with a headache, pains in the stomach, vomiting and stiffness of the neck. Upon admission he was suffering from marked stiffness of the neck and back. During the following days he grew increasingly

Table  
*Spinal Fluid-Blood Quotient in*

No.	Age	Condition at determ. of quotient	Lumbar puncture at determ. of quotient				No. of days between admittance and det. of quot.	Dose
			Cells		Alb.	Glob.		
			Numbers	Kind				
1	60	I	3500/3	50 % poly	30	0	2	g 1×8
2	8	II	10400/3	poly	40	2	4	g 1×6
3	22	II	1236/3	poly	30	3	2	g 1×8
4	21	III	2250/3	poly	50	4	2	g 1.5×6
5	12	I	3000/3	poly	30	3	2	g 1×6
6	2	I	10000/3	poly	20	2	1	g 0.5×8
7	14	I	500/3	50 % poly	20	0	3	g 1×6
8	21	I	130/3	mono.	10	1	3	g 1×6
9	21	III	26600/3	poly	200	20	1	g 1×8
10	21	I	134/3	mono.	10	0	6	g 1×6
11	20	I	80000/3	poly	30	0	2	g 1.5×6
12	36	III	100000/3	poly	90	0	1	g 1.5×6
13	27	II	34/3	50 % poly	40	1	1	g 1×8
14	29	I—II	2016/3	poly	40	2	2	g 1×8
15	18	II	20800/3	poly	100	9	1	g 1×6
16	28	I	680/3	75 % poly	20	0	1	g 1×8
17	29		1670/3	poly	10	0	1	g 1×6
18	3	II	5280/3	poly	40	2	4	g 1×6
19	23	I	3200/3	poly	40	4	1	g 1×6

On the other hand, in the remaining two patients with a quotient exceeding the normal range the course of the disease clinically differs so much from what is usually seen that a brief report of the case history may be of interest.

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1.1	1.1	3.2	4.6	0.34	Bact. not found.
1.9	2.2	5.0	6.8	0.38	Growth of Meningoc. Very ill, Paresis of the facial nerve.
0.6	0.6	1.7	3.0	0.35	Growth of Meningoc.
1.9	2.2	9.1	9.8	0.21	Bact. not found.
3.0		7.2	10.7	0.42	Growth of Meningoc.
1.9	1.9	4.7	6.0	0.41	Growth of Meningoc.
1.3	1.5	3.9	4.7	0.33	Bact. not found.
1.6	1.8	5.1	6.2	0.31	
2.1		6.4	9.5	0.33	Growth of Meningoc.
1.0	1.0	3.4	3.5	0.29	
1.6		5.0	6.4	0.32	Growth of B. Pfeiffer. Died on 30th day after det. of Quot.
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Table  
*Spinal Fluid-Blood Quotient in Patients with*

No.	Age	Diagnosis	Ad- mit- ted	Date	Lumbar puncture			
					Cells		Alb.	Glob.
					Numbers	Kind		
1	21	Meningitis cerebr. epid.	9/9	9/9	96000/3	poly	200	20
				10/9	26600/3	poly	200	20
				22/9	537/3	m	80	4
				9/10	68/3	m	80	4
2	36	Meningitis cerebr. epid.	8/10		70000/3	poly	not determined	
				9/10	100000/3	poly	90	0
						70 %		
			11/10		1528/3	poly	50	2
			17/10		119/3	m	40	2
3	27	Meningitis cerebr. epid.	26/10	26/10	5760/3	poly	not determined	
						50 %		
				27/10	34/3	poly	40	1
				30/10	202/3	m	30	0
4	19	Meningitis cerebr. spin. Syphilis	8/11	7/11	60000/3	poly	not determined	
				9/11	2016/3	poly	40	2
				15/11	142/3	m	30	1
				25/11	70/3	m	10	0
5	18	Meningitis cerebr. spin. epid.	20/11	21/11	10850/3	poly	100	9
				25/11	130/3	m	10	0
				1/12	45/3	m	10	0
6	29	Meningitis purul.	15/2	16/2	12800/3	poly	too little	too little
				17/2	1670/3	poly	10	0
						80 %		
				19/2	170/3	m		
7	23	Meningitis purul. sinuitis front.	4/5			overv.		
				5/5	420/3	poly	30	2
				7/5	3200/3	poly	40	4
				10/5	27/3	m	not determined	
8	3	Meningitis purul. Pfeiffer	11/10	11/10	204000/3	poly	80	7
			11/10	15/10	5280/3	poly	40	2
				20/10	324/3	poly	30	1
						60 %		
				1/11	126/3	poly	10	1

## VII.

*Purulent Meningitis, observed for some Time.*

Degree affected	Dose	Sulfathiazole Conc. in mg %				Quot.	Comments
		in sp. fluid		in blood			
		free	total	free	total		
III							Recovery
III	g 1×8	1.9	2.2	5.0	6.8	0.38	
II	g 1×6	1.0	1.0	2.2	3.2	0.45	
II	g 1×6	1.1	1.1	5.3	6.0	0.21	
III	g 1.5×6						»
III	g 1×6	3.0		7.2	10.7	0.42	
I	g 1×6	1.6	2.0	6.1	8.1	0.26	»
I	g 1×6	1.1	1.2	6.8	6.8	0.16	
I	g 1×8						»
II	g 1×8	1.9		4.7	6.0	0.41	
I	g 1×8	1.4	1.4	8.2	9.1	0.17	
I—II	g 1×8	1.3	1.5	3.9	4.7	0.33	»
I	g 1×4	1.0	1.1	3.7	4.6	0.27	
I	g 1×4	0.8	0.9	4.3	4.4	0.19	
II	g 1×8	1.6	1.8	5.1	6.2	0.31	»
I	g 1×4	1.3	1.3	3.8	4.9	0.34	
I	g 1×6	0.9	0.9	5.5	6.7	0.16	
III							»
II	g × 6	1.0	1.0	3.4	3.5	0.29	
I	g 1×6	0.7	0.7	4.1	4.6	0.17	»
I	g 1×6	1.5	1.6	5.1	6.7	0.29	
I	g 1×8	1.7	1.9	6.6	8.0	0.26	
I	g 1×6	1.5	1.6	4.8	6.6	0.31	
III	g 1/2×6						»
II	g 1/2×6	1.6		5.0	6.4	0.32	
II	g 3/4×6	0.9		3.7	4.8	0.24	
II	g 1.2×6 rectally	0.5	1.3	1.7	0.38		Died 13/11-41

Table  
*Spinal Fluid-Blood Quotient in Patients with*

No.	Age	Diagnosis	Admitted	Date	Lumbar Puncture			
					Cells		Alb.	Glob.
					Numbers	Kind		
1	31	Poliomyelitis Febr. rheum. Endocard. rheum. Tonsillitis chr.	6/9	6/9	256/3	m.	10	0
				13/9	13/3	m.	10	0
2	6	Poliomyelitis ant.	26/10	26/10	256/3	m.	10	0
				27/10	76/3	m.	10	too little
3	7	Poliomyelitis ant.	18/8	18/8	185/3	m.	30	1
				10/9	10/3	m.	20	1
4	3	Poliomyelitis ant.	1/9	4/9	19/3	m.	10	0
5	13	Poliomyelitis ant.	26/8	30/8	2288/3	m.	60	2
				4/9	768/3	m.	60	2
				26/8	2416/3	m.	60	2
6	13	Polyradiculitis ac. infect.	15/6	19/6	46/3	m.	20	2
7	24	Polyradiculitis ac. infect.	26/8	1/9	22/3	m.	50	2
8	27	Polyradiculitis ac. infect.		16/1	156/3	m.	10	0
9	27	Polyradiculitis ac. infect.	12/1	12/1	306/3	m.	10	1
				15/1	156/3	m.	10	0
10	45	Encephalitis prim.	17/2	24/2	63/3	m.	30	5

clouded and groping. The cell count in the spinal fluid was on the increase and everything seemed to indicate that it was a case of tubercular meningitis, especially since the L. B. Q. was 0.37.

Examination of the eyes showed papillary edema without prominence of the disk. The neurological examination revealed

## -VIII.

*Poliomyelitis, Polyradiculitis and Encephalitis.*

Degree affected	Dose	Sulphathiazole Conc. in mg%				Quot.	Comments
		in sp. fluid		in blood			
		free	total	free	total		
I							
I	g 1×6	0.6	0.6	4.0	4.2	0.15	Died 28/10 from respiration paralysis. Sect.: Poliomyelitic changes in med. obl.
II	g 1/2×6	0.9	1.0	5.4	6.5	0.18	Cannot hold head up. (27/10).
II	g 1/2×6	0.6	0.7	5.8	8.0	0.11	Paresis of right arm.
II		1.1	1.3	4.9	8.2	0.22	Slight paresis of lower extrem.
I	g 3/4×6						
II	g 3/4×6	0.8	0.8	2.6	4.3	0.32	Facial paresis.
II	g 3/4×6	0.8		5.5	7.4	0.15	Facial paresis.
I	g 3/4×6	0.6	0.6	2.1	3.0	0.29	
II	g 1×6	0.8	0.8	2.7	4.5	0.29	Reduction of power in upper extr.
	g 1×6	0.4	0.4	1.5	2.0	0.27	
II	g 1×5						
II	g 1×5	0.4	0.4	1.5	2.0	0.27	Slight paresis of upper extr.
II	g 1×6	1.5	1.7	2.8	3.7	0.53	Died 20/3. Sect.: Encephalitis? No sign. of Tub. No exudate in membranes.

nothing special, particularly no reflex changes. Conclusion of the neurological examination: »It is presumably a case of particularly severe endemic arachnoiditis.« All the other tests and blood samples yielded nothing.

A fortnight after admission, however, the symptoms began to clear up, and after another three weeks he was discharged fully



restored. In this case the quotient dropped simultaneously with the improvement in the clinical condition.

There can be no doubt that the two cases here reported differ essentially from the usual course of lymphocytic meningitis. It is of rare occurrence in this country that a patient with primary lymphocytic encephalo-meningitis presents a general condition so much affected as in the cases reported, but in this connection it is of importance to recall that the diagnosis »lymphocytic meningitis» is a lumber-room diagnosis comprising all cases of meningitis with lymphocytic pleocytosis in which the infectious agent cannot be demonstrated. It might therefore be expected at the outset that this group of diseases would comprise a heterogeneous collection of pathological pictures from the milder to the more severe cases, and it is of interest to note that severe cases of lymphocytic meningitis too may be connected with such a severe lesion of the meninges that the permeability of the blood-fluid barrier undergoes a change. The cases cited are also a demonstration of the fact that a rise in the quotient in a lymphocytic meningitis is not specific to tubercular meningitis, which, indeed, was not to be expected.

A considerable increase in the quotient, and especially an increase that mounts during the course of the disease will, however, as pointed out already, speak strongly in favour of the diagnosis tubercular meningitis in patients with a lymphocytic meningitis.

Conditions in the purulent cases of meningitis will appear from Table VI.

Amongst other things the table shows the spinal fluid findings upon admission. Besides the result of the quotient determination the condition at the time when the quotient was determined is also entered and the number of days elapsed between admission and determination of the quotient. As will appear from the table, the quotient was determined in nearly all cases shortly after admission at the time when the meningitis was in its most severe phase.

It will be seen that the quotient ranges from 0.15 to 0.51. On the whole, however, the quotient is considerably increased, with a mean value of 0.33.

As might be expected, purulent meningitis with the severe intensive changes in the meninges produces an essential change in the permeability conditions of the blood-fluid barrier. It appears, however, that the changes in permeability are not so radical here

as in the other intensive form of meningitis, tubercular meningitis, which showed a mean quotient of 0.42.

The table shows that there is not in the individual investigation any sure proportionality between the height of the quotient and the clinical condition of the patient, or between the quotient and the content of cells and proteins in the spinal fluid.

As regards the absolute concentrations it is seen that they vary between the following values: in the blood between 9.4 and 2.3 mg % for the free compound and between 12.0 and 2.9 mg % for the total amount.

The mean value is 4.8 and 6.4 mg % for the free and the total amounts respectively. In the spinal fluid the values for the free compound vary between 0.6 and 3.0 mg % with a mean value of 2.0 mg %. The total amount in the spinal fluid is a trifle higher, but the determination was not made in all cases, so the mean value has not been computed. The concentrations obtained were in all cases sufficient to bring about restitution except in one case (No. 18) where the meningitis was caused by the chemotherapeutically but slightly affectible B. Pfeiffer.

Table VII shows the result of a series of concentration determinations on patients with purulent meningitis where the increased quotient has been determined repeatedly during the course of the disease. It appears that the quotient decreases about simultaneously with the improvement in the patient's condition and with the spinal fluid findings. In one case (No. 7) the quotient is slightly mounting, despite the improvement in the patient's condition, and in one case (No. 8) a steadily rising quotient was observed, (the patient who died from his Pfeiffer meningitis.)

In the height of the quotient we have presumably an approximate expression of the severity of the lesion in the meninges, although there is hardly direct proportionality between the two factors. There is, however, a remarkably good agreement between the quotient and the clinical condition of the patient.

Finally Table VIII shows the result of the determination of the quotient in a number of patients with various infectious diseases of the central nervous system, predominantly paralytic poliomyelitis.

It will be seen that in one of the cases a moderate increase in the quotient was found in a case of poliomyelitis. In the other 4 cases the quotient was normal.

The patients with poliomyelitis all showed a moderate and rather uniform increase (0.27—0.29), and finally the patient who died of encephalitis showed a very considerable increase in the quotient.

Of the more detailed mechanism as regards the variations of the quotient our present work furnishes no information.

Investigations on the form in which sulfathiazole occurs in the blood (Harrestrup Andersen, Møller and Simesen, 1942) have, however, given the result that besides in a free and acetylated form sulfathiazole is found in the blood in an ultra-filterable and a non-ultrafilterable form, that is to say in 4 forms in all.

If it be assumed that normally only the filterable form is able to pass the barrier, this will explain the difference in concentration in the blood and the spinal fluid respectively, in normal persons.

Injury to the barrier should afford a possibility for the passage also of the non-filterable part of sulphathiazole (which is presumably protein-fixed) into the spinal fluid, which causes a rise in the L. B. Q. The investigations in the above-mentioned work on the filterability of sulphathiazole into the spinal fluid of patients suffering from non-tubercular, lymphocytic, and purulent meningitis respectively favour this theory.

In the first-mentioned case 100 % of the sulphathiazole in the spinal fluid was filterable, in the last-mentioned case there was a non-filterable residue.

According to this theory it might be expected that, if the non-filterable part of the sulphathiazole were protein-fixed, the quotient in the cases with injury to the barrier would be proportional to the protein content in the spinal fluid. As will appear from our investigations, this is not the case.

Whatever the explanation of the results obtained, there can hardly be any doubt that determination of the quotient gives a better expression of the injury to the barrier than albumin and globulin determinations.

## Conclusion.

I. The investigations showed a considerable rise in the blood-liquor-quotient for all the patients suffering from tubercular meningitis.

II. In the other patients examined who were suffering from lymphocytic encephalomeningitis, a moderate rise in the quotient was found in some few cases only, and predominantly in patients severely ill.

III. An essential and especially lasting rise in the quotient in a patient with lymphocytic meningitis is therefore a very strong indication that the meningitis is of tubercular origin.

IV. In polyradiculitis and poliomyelitis a moderate rise in the quotient may occur. The increase is, however, considerably lower than in patients with tubercular meningitis.

V. In patients with purulent meningitis there is in most cases a considerable increase in the L. B. Q. The increase in the quotient in the main subsides simultaneously with the improvement of the clinical condition.

### Summary.

The permeability conditions in regard to the blood-fluid barrier are briefly reviewed.

Previous investigations have shown that in normal persons the quotient sulfathiazole in the spinal fluid: sulfathiazole in the blood lies at a level of about 0.20. These investigations are confirmed.

Upon examination of 9 adults and 11 children suffering from non-meningeal affections the mean quotient was determined at 0.17, ranging from 0.12 to 0.22.

Upon examination of 10 patients suffering from *tubercular meningitis* an increase in the quotient averaging 0.42 was found in all cases, ranging from 0.32 to 0.55.

In 9 patients suffering from secondary lymphocytic meningitis a normal quotient was found (mean value: 0.18, varying between 0.14 and 0.23).

In 9 patients suffering from primary lymphocytic meningitis a moderate increase was found in 2 cases. The increased quotient, however, dropped to normal in the 2 cases in which the patient was kept under observation until restitution. The remaining cases showed a normal quotient.

In patients with polyradiculitis a slight increase was found, and in patients with poliomyelitis a slight or no increase.

As the result of the investigations it may be established that in patients suffering from lymphocytic meningitis an essential and especially lasting increase in the quotient (above 0.30) is a very strong indication that the meningitis is of a tubercular nature.

### Litterature.

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## Emphysema Pulmonum Bullosum.

By

PAUL OWREN.

(Submitted for publication November 30, 1942).

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The presence of emphysemateous bullae in the lungs is generally a finding incidentally recorded at x-ray examinations and post-mortems. On the x-ray picture they may assume the shape of ring-formed shadows, an appearance that often causes diagnostical difficulties. Their chief clinical interest lies in the fact that, on bursting, they may occasion a pneumothorax.

According to Laurell, the emphysemateous bullae are mostly located under the pleura or between the lobes. It is very rare to find them spread in the parenchyma in such a degree as to provoke clinical symptoms, and in this case the relation to cystic lungs of other origin is not clear.

From later years we have descriptions of some cases of sub-pleural emphysemateous bullae of such dimensions that they have provoked clinical symptoms by their size only, quite mechanically. (1. 4. 6. 7. 8. 9. 10. 11. 14. 17). Most of the authors restrain themselves to the discussion of the difficult roentgenologic diagnosis, especially with regard to pneumothorax. As to the etiology and the pathogenesis of the disease, the opinions are divergent.

In the following statement, three new cases of a similar affection are referred. In one of them patho-anatomical examination of the lungs was performed, the affection being a bilateral one with lethal

issue. This case in particular it is hoped may furnish some new elements to the comprehension of the clinical picture and pathogenesis of the illness.

From corresponding cases earlier described, results from autopsy were only available in one single case.

*Case 1.* A 50 years old instrumentmaker.

The pat. had been somewhat exposed to inhalation of dust in his work, though not in any marked degree.

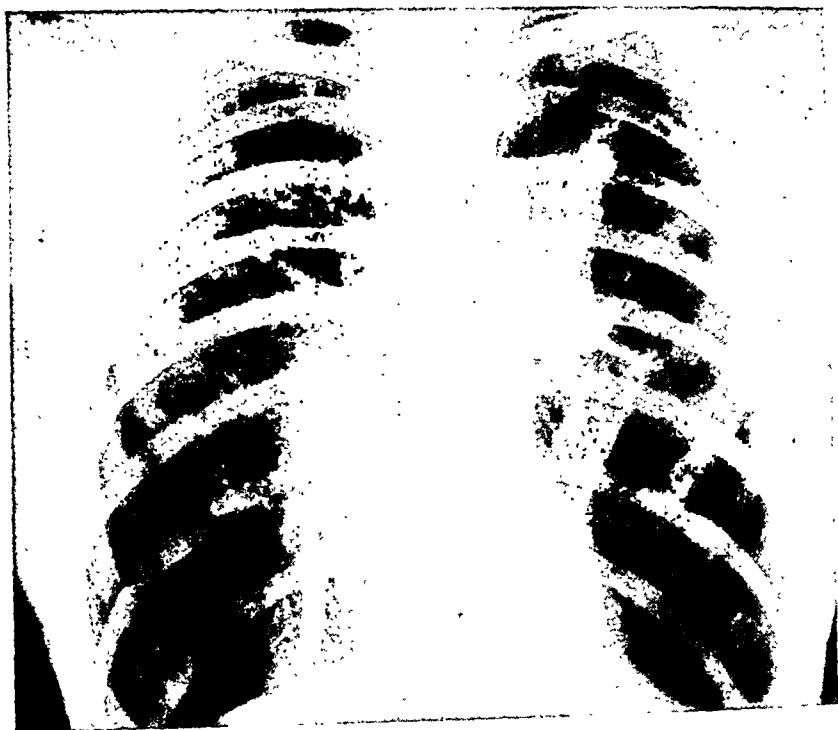


Fig. 1.

In 1925 his chest got squeezed against a screw and he was incapacitated for 3 weeks. Otherwise sound until 1938. Suddenly, in the spring of 1938, without any apparent reason, he felt a stitch and violent pains in both sides of his chest with severe dyspnoe and a feeling of suffocation. The attack lasted for about one hour, and since then he has suffered from a persisting dyspnoe on exertion. In the spring of 1939 he had another attack, and yet another in the summer of 1940, of exactly the same nature as the first, his dyspnoe on exertion getting worse after each attack. In the spring of 1941, the attacks became more frequent and his dyspnoe forced him to keep quiet as much as possible. He was hospitalized in the Service in september 1941.



Fig. 2 a.

*Signs and symptoms on admittance:* Cyanosis with fast pulse. Strikingly pronounced dyspnoea on the slightest effort. Thorax in permanently overexpanded position with extended use of auxiliary respiratory muscles on inspiration. Further: inspiratory withdrawal of the epigastrium and of the intercostal space over the nether part of the thorax, the costal arch joining in the movement. During this paradoxical movement of the nether aperture of the thorax, the circumference on this point diminished by 2 cm. Evidently the lower portions of the lungs were not taking part in the respiration. The physical examination further revealed symptoms of a pneumothorax on both sides with inaudible breathsound and a deep, strong, «hyperresonant» percussion note that reached below the 12th rib; heart- and liverdullness were missing. Vital capacity 900 cm<sup>3</sup>. Pirquet —. Globular sedimentation rate normal.



*X-ray examination* (fig. 1): Full «clearing-up» at the base on both sides without lungmarkings. Indistinct boundary towards the structural pulmonary tissue. No ringformed shadows were to be seen, denoting possible emphysemateous bullae elsewhere in the lungs; an interesting fact compared with the results at the section.

*Bronchography:* The bronchial branches were pressed together in the area near hilus, on both sides. The bronchial lumina were slightly reduced in size; no local stenosis. None of the opaque agent had penetrated into the supposed emphysemateous bullae.

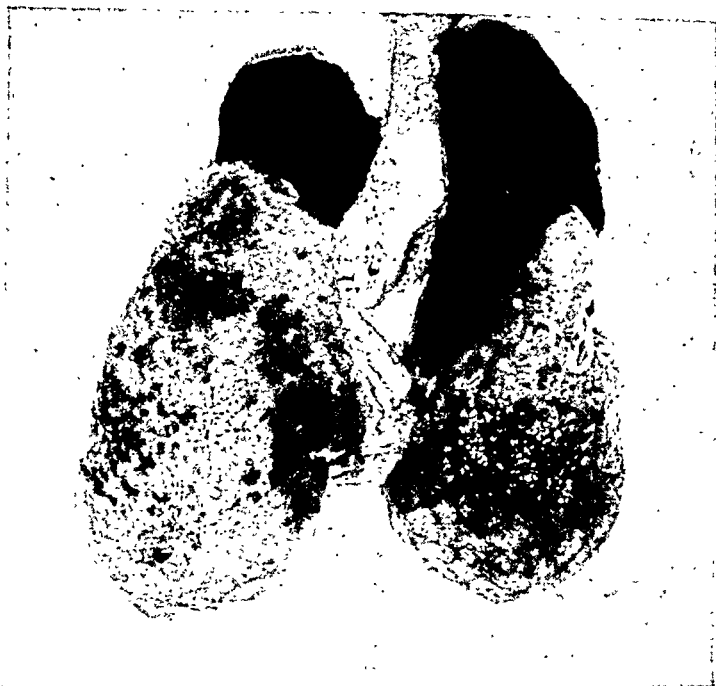


Fig. 2 b. (superior lobes artificially blackened on the photo.)

*Bronchoscopy:* Normal findings.

The patient grew steadily worse with increasing dyspnoe and frequent choking attacks. He died after one month, his respiratory difficulties becoming ever worse.

*Patho-anatomical investigations.*

The aspect of the lungs may be seen on fig. 2 a—b. The emphysemateous bullae at the base occupied almost the entirety of the inferior lobes. Besides smaller bullae of different size, a subpleural emphysema was revealed with small blebs, which does not come out so well on the plate. The portion left of the nether lobes was atelectatic, the rest of the lungs being aerated without nodes or infiltrations. A roentgenogram (fig. 3) of the extirped breastorgans illustrate the reciprocal size of the bullae. The inward aspect of the bullae (fig. 4) proved them to be emphysemateous;



Fig. 3.

not of cystic origin. The parenchyma was pressed together below their central parts and atelectatic, while towards the periphery it was dissolved in largemeshed emphysema, where a meshwork of threads and membranes reached from the lungs to the pleura. This meshwork was made out of the remnants of the alveolar walls and septa with partly obliterated vessels. On further examination of the bronchial tree, with renewed bronchography of the extirped lung, and macroscopic examination with splitting up of the bronchia, no narrowing or stenosis were found neither in the larger nor in the smaller bronchia. All the larger bullae had a valvular structure, the air passing easily in, but being impossible to squeeze out.

No visible bronchial openings were leading to the bullae. On insufflation the air streamed in on several points, especially through the loose peripheric tissue. By segregation of the bronchial branches, one could localize the valvular mechanism peripherally to the small bronchia, as far as these could be pursued.

To the elucidation of the nature of the valvular mechanism the following facts were stated: On experimental in- and exsufflation through the adductiv bronchia, the valvular effect proved to persist after the opening of the bullae, but could be suppressed by removal of the degenerative pulmonary tissue at the bottom, in the places of communication. This tissue thus seemed capable of provoking a valvular effect.



Fig. 4.

A bronchogram (fig. 5) from the peripheric part of a large bulla furnished the following data: The bronchial branches run alongside the wall of the bulla, the bronchial tree being to some extent split in two by the bulla lying in the middle. Consequently, smaller bronchia and bronchioli will be exposed to lateral pressure from the bulla. In these circumstances the normal inspiratory extension and expiratory contraction of the bronchia, together with the compressive effect exercised by the bulla (strongest at the expiration, less strong at the inspiration) must equally be considered as susceptible of releasing a valvular effect.

Within the bulla the pressure will be positive, except on the height of the inspiration, when it will approach zero. This pressure will thus contribute to increase the atelectasis below the central parts of the bulla, stretching the parenchyma peripherally along the pleura, by which process the



Fig. 5.

vessels become anaemic and the parenchyma degenerates. The growth of the bulla thus causes the pleura to be peeled off the lungs, so to speak.

Smaller bronchia and bronchioli in the atelectatic zone were seen to be pressed together and did not communicate with the bulla. During the growth of the bulla, new bronchial communications will open peripherally, while the former openings will be closed towards the centre, in proportion as they are swallowed up by the atelectatic zone. The rapidity of the growth will depend on the effectivity of the valvular mechanism, and the resistance of the pulmonary tissue to the pressure.

The microscopic examination further revealed insignificant fibrosis, probably of secondary origin. No signs of silicosis.

Alterations of the vessels were noted in several places, such as mesarteritis with extended infiltration of lymphocytes, partly in the shape of pronounced proliferation of the intima with a narrowing of the lumen, in some places even with infiltration of adventitia. Otherwise there were no signs of infection.

Vascular alterations will always be apt to provoke a disposition to emphysema, through disturbance of the metabolism. In this case it was difficult to decide which symptoms were of primary and which of secondary origin; but at all events such alterations of the vessels will contribute to hasten the progression of the disease by reducing the faculty of resistance of the parenchyma.

The next two patients who have been treated in the Service lately, offer a clinical and roentgenological picture which, with our knowledge of the first case in mind, proves that we have to deal with the same affection.

**Case 2.** A 19 years old volunteer. Previously healthy. Suddenly, in may 1932, without preceding exertion, he got such violent pains and stitches

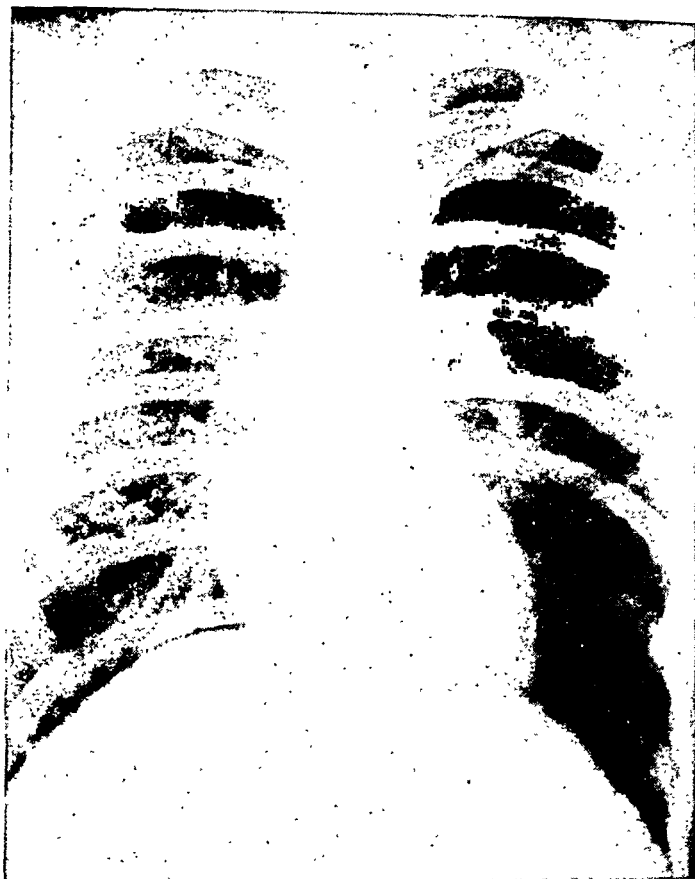


Fig. 6.

in the left part of the thorax, that he had to be helped to bed. After a week he was again free from symptoms. He had no cough. In the course of the following years he noted a stitch and pains in the same spot, usually lasting a day's time, mostly in connection with stronger efforts. After a skiing expedition in 1938, his state grew worse, with ever more frequent attacks and continuous dyspnoe on exertion. Hospitalized in the Service the 10th. of June 1938.

*Signs and symptoms on admittance:* Breathsound inaudible over the nether part of the left lung with deep enforced percussion note as by pneumothorax. Pirquet —. Sedimentary rate normal.

*Roentgen* (fig. 6): The pulmonary area at the base of the left lung abnormally clear without vesselmarkings. Diaphragma-vault flattened out. It was not possible to distinguish any bounding outlines of the lung that could furnish a foundation for the suspicion of a pneumothorax. A lateral picture proved the aeration to be localised backwards. Probable diagnosis: Subpleural emphysemateous bulla (Prof. Dale). *Bronchogram* (fig. 7): Distal bronchia pressed together and contrastfilled alveolae in the left lower

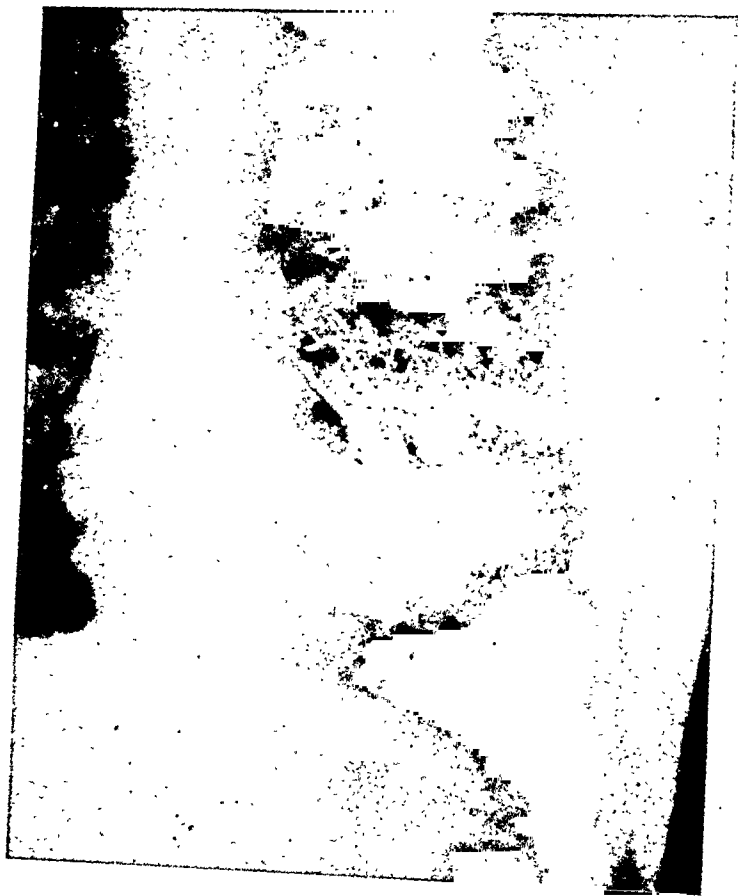


Fig. 7.

lobe. No localised bronchostenosis. None of the opaque agent passed out into the clear parts.

A diagnostical pneumothorax was carried out. Pleural pressure  $-6-4$ , by deep respiration  $-10-0$ . After insufflation of  $250\text{ cm}^3$  air, the final pressure was  $-4-0$ . About 7 hours later, the patient got worse with dyspnoe, tachycardia and distorting pain. Physically there were signs of total pneumothorax. An x-ray examination (fig. 8) revealed, besides the pneumothorax, that the earlier observed clearing-up was localised within the borders of the nether lobe, with a delicate lateral margin. The diagnosis of emphysemateous bulla seemed thus confirmed.

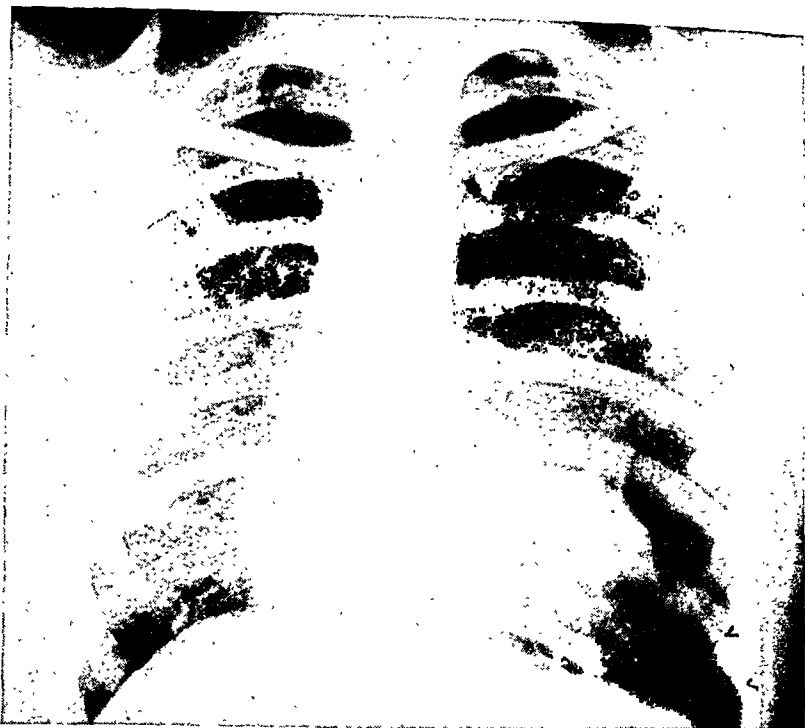


Fig. 8.

*Thoracoscopy* (Dr. med. Ustvedt): The emphysemateous bulla was lying as a pulmonary lobe of the size of a babe's hand, on the posterior part of the diaphragma-vault. The surface had an appearance like that of the lung itself and pleura was normal.

The pneumothorax was resorbed in the course of a month's time. Since then the pains have been about the same as before the pat. was subjected to treatment, with moderate dyspnoe on exertion, and from time to time attacks with stitch and pain in the left side on stronger efforts. He still has no cough. Control by x-ray proves the emphysemateous bulla to have varied somewhat in size in course of the elapsed years, though on the whole without any sure-increasing tendency.

**Case 3.** A 53 years old seargent.

The pat. noted his pulmonary disease for the first time in 1936 when, in connection with a cold, he had attacks of dyspnoe accompanied by distorting pains in the breast. Since then he has suffered from a persistent dyspnoe on exertion that has varied somewhat from time to time, but on the whole has increased from year to year. He has had some periods with fever, cough and expectoration, and was then especially tormented.

In March 1939, a roentgenological «clearing-up» was found at the base of both lungs. The breathsound was strongly reduced downwards posteri-



Fig. 9.

only on both sides. Vital capacity 3800 cm<sup>3</sup>. In April 1942, when he was hospitalised in the Service, the examination furnished the following data: Inaudible breath sound posteriorly on both sides below spina scapulae, with deep, enforced «hyperresonant» percussion note. The X-ray examination now revealed a large basal clearing-up without lungmarkings on both sides, remarkably larger than in 1939. On the left side no distinct boundary towards the structural pulmonary tissue, on the right side could be seen the outlines of a large bulla (fig. 9). Vital capacity 1500 cm<sup>3</sup>. Thus, in this case, a pronounced progression of the affection had taken place in the course of the last year.



## Discussion.

All three patients present a clinical and pathological picture, as well as roentgenological findings, supposed to be characteristic of the bullous pulmonary emphysema. The chief symptom is dyspnoea, accounted for by the anatomical discoveries. This shortness of breath will manifest itself in proportion to the size of the emphysemateous bulla — which reduces the respiratory capacity of the parenchyma consequentially — together with the altered circumstances of pressure. Changes in the circulation will ultimately contribute to increase the dyspnoea.

Receding attacks of pain in the breast, accompanied by increasing want of breath, seem to be characteristic. These symptoms do not declare themselves in all cases however. They are provoked by a forced respiration, and find their explanation in an acute overfilling of air and increased pressure in the bullae, the filling of which is directly dependent on the deepness of the inspiration. It is probable that the valvular mechanism works more or less effectively at different times, and thus influences the size of the bulla (cf. the 2. case), the subjective sensations and the tendency to attacks.

The pathogenetic mechanism that produces the emphysemateous bullae in these patients, seems to be quite different from that of the so-called »scartissuebullae» (Spitzennarhenblasen), or vesicles in the connecting tissue. These appear, as one knows, in chronic inflammations with development of connecting tissue (tuberculosis, silicosis etc.), where scarshrinking occasions valves to be formed in the bronchioli. (Hayashi, Fischer). The emphysemateous bullae are in such cases as a rule relatively small, although some »giant bullae» have been described in cases of anthraco-silicosis (Wiese et al.). It is equally well known that valvular stenosis, expiratory valvular mechanisms in smaller or larger bronchia, provoke emphysema in corresponding parts of the lung. Such cases may occur in almost every affection of the lungs, and play surely a greater part in the development of different pathological cavities than earlier suspected. If such a valvular stenosis is sufficiently stable and persistent, the emphysema may assume a bulleous character through subsequent atrophy and confluence.

Bronchography has effectively, in some of the earlier referred cases of localised bulleous emphysema, evidenced insufficient

filling and narrowing of the bronchial lumina, sometimes obvious bronchial stenosis (Westermarck). This type of secondary bulleous emphysema, based on a fibrous-pulmonary affection or an organic bronchial stenosis of other genesis, stands pathogenetically in the same class as Fischer-Wasel's vesicles in the connective tissue. The fact that they so seldom attain larger dimensions, is probably due to fibrosis, which in itself constitutes a hindrance to the growth of the blebs.

Contrary to this secondary form, the affection manifests itself in other cases, as in those of our patients, as an apparently primary malady, without subjectively or objectively traceable signs of previous lung lesions.

Even a patho-anatomical examination (case 1), revealed no signs of any other disease, especially no infection, fibrosis or organic bronchial stenosis, capable of explaining the genesis of the emphysema.

The nature of the degenerative parenchyma, and the general spreading of the affection, as in several earlier referred cases (1. 4. 9. 11. 16) and in our first and third case, make it probable that the primary cause of the disease lies in the parenchyma and that it is due to a general abnormality of the lungtissue itself, especially in the subpleural zone. Whether this weakness is congenital or acquired is impossible to ascertain. It may be that vascular alterations play a part. This hypothesis is corroborated by the fact that the changes in view are chiefly localised under the pleura. Experimental investigations proved that the valvular effect is brought about, not by any organic changes in the bronchiae or by scarretractions, but by a functional mechanism — in which the variations in pressure during the respiration play the chief part — in connection with the degenerative parenchyma at the bottom of the bullae. The greater the bulla, the more effective will be the valvular mechanism, in reason of the direction imposed upon the bronchiae and of the conditions of pressure. This valvular mechanism is important for the progression of the disease and for the occurrence of attacks, but the primary and essential condition seems to lie in the pulmonary tissue being abnormally disposed to degenerate.

It is also possible that the cases of this affection described as localised forms, have had a wider spreading than expressed on the roentgenograms.

According to Laurell, on the other hand, an emphysemateous bulla of some cms.' diameter should provoke visible changes in the roentgenogram, but it occurs equally often that subpleural emphysemateous bullae are considerably larger, without occasioning any roentgenological changes (cfr. case 1). In some of the previously referred cases, one has evidence of protracted chronic bronchitis, and the part played by the bronchitis as etiologic factor is discussed. In the first as well as in the second case referred in this paper, this eventuality can be disregarded, no sign of infection having been discovered.

As to the *diagnosis*, the physical findings are the same as by pneumothorax, as already stated, and roentgenologically the similitude is very great. Demonstration of the atelectatic zone, and an indistinct boundary towards the structural pulmonary tissue are important diagnostic hints.

It is not advisable to proceed to the measuring of pressure, or to make a trial with diagnostical pneumothorax as in our second case. (J. Lewis interpreted his patient's condition as a doublesided pneumothorax and proceeded to measure the pressure on both sides at a time. The patient died some hours later).

It stands to reason that an internal treatment of this disease can scarcely count upon any striking results. Our two last patients noted a passing relief from their dyspnoe by use of ephedrinmedicaments.

The most rational treatment no doubt would be lobectomy, where the condition of the pat. otherwise should allow such an intervention. Relapses may not be improbable however, because of the general character of the affection.

Theoretically, the patient might be saved out of the dangerous situation by the provoking of an artificial stenosis of the adducting bronchiae to the larger bullae. But the experimental trials hitherto made in order to bring about an artificial stenosis in the bronchiae, have not as yet led to any sure and practically useful methode.

### Summary.

The bulleous pulmonary emphysema appears partly as an attending pathological phenomenon of secondary progeny in fibrous lung-diseases and protracted bronchial valvular stenoses, partly as an

apparently primary affection without any other demonstrable preceding or attending maladies. The author refers three cases of this last type, one with lethal issue. Taking his point of departure in the pathoanatomical and experimental investigations of this latter case especially, the author comes to the following conclusions:

1. The primary cause of the illness is to be found in a general abnormality of the pulmonary tissue, acquired or congenital.

2. The emphysematous bullae manifest a character of valvular blebs, with multiple valvular mechanisms that are constantly formed and deformed in the course of the growth of the bulla. The degenerative lungtissue at the bottom of the bulla is of importance to the generation of the valves, that are provoked by variations in pressure during the respiration.

3. The changes in the bronchiae demonstrable on x-ray pictures in this last type of the affection, are of secondary genesis.

*Added under the correction of the proofs.*

Pat. nr. 3 was anew hospitalized in the Service on the 14. of February 1943, with a violent attack of dyspnoe, and died within 24 hours.

While he was dying, it was proceeded to a measuring of the pressure in the large bulla on his right side, in spite of the risque of provoking a pneumothorax. Initial pressure  $+10 - 0$ . After exsufflation of  $350 \text{ cm}^3$  the pressure sank to  $-8 - 2$ . In the course of 5 to 10 min. the pressure mounted anew to zero, and further to  $+5 - 0$ , a fact that confirmed the presence of a valvular mechanism in the bulla. The post-mortem revealed large emphysematous bullae at the base of the lungs, and an extended subpleural emphysema. No pneumothorax. The patho-anatomical investigations confirmed the observations earlier referred.

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From the Dermatological Clinic of the University of Oslo (Rikshospitalet)  
Chief: Professor dr. med. N. Danbolt.

## On Kveim's Reaction in Boeck's Sarcoid.

By

N. DANBOLT.

(Submitted for publication February 4, 1943).

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In N. M. 1941: 9: 169 A. Kveim has given a preliminary report of a new, specific cutaneous reaction in Boeck's sarcoid.<sup>1</sup> While he was assisting physician at the Dermatological Clinic of the Rikshospital, Kveim made a thorough study of a number of patients with Boeck's sarcoid and the results of this examination will be published, probably in 1943, as a supplement to *Acta Dermatovenereologica* (academic thesis).

Since Kveim left the Dermatological Clinic we have continued investigations on the new cutaneous reaction and its clinical significance, and in this paper I shall give an account of some of the observations which have been made in the course of the last 2 years.

The antigen is produced as described in Kveim's publication. Sarcoid tissue, preferably a lymph gland, is crushed under sterile conditions and carefully mixed in a mortar with physiological saline and diluted with saline to about 1: 10. This mixture is then filtered through gauze and sterilized by heating in a water bath to 60° for 2 hours, twice, at intervals of 24 hours (during the interval the mixture is kept in a thermostat). After the sterility has been controlled (by inoculation on blood-agar and broth) and after the addition of 0.5 % carbolic acid, the mixture is distributed in ampullae in quantities of 0.2—0.5 cm<sup>3</sup>. Before use the ampullae

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must be shaken well, after which the fluid is drawn up into a hypodermic needle (not too finely pointed) and the antigen is injected *intradermally* in the skin of the anterior side of the lower arm in a quantity of 0.1—0.2 cm<sup>3</sup>. The point of injection is marked and controlled for *weeks and months*.

In the course of the first few days the skin changes caused by the needle and the mechanical effect of the injected mass disappear. In healthy individuals (the reaction has been performed upon A. Kveim and the present author inter al.) no changes in the skin have appeared at the point of injection after weeks, months and even years. In the course of the last 2 years Kveim's reaction has also been performed on 16 patients *not* suffering from Boeck's sarcoid (5 of these had lupus vulgaris) and in all these cases the reaction was negative.

The continued investigations on the specificity of the reaction have thus given results in agreement with those observed by Dr. Kveim. There has not been a single case of a positive reaction in patients with diseases which after clinical investigation must be assumed to have *no* connection with Boeck's sarcoid. In one case of lupus miliaris disseminatus faciei there was a doubtful positive Kveim's reaction. But as this is a disease which may be closely related to Boeck's sarcoid, the case will not be described in the present publication.

I shall give an account of the result of the reaction in *10 cases of Boeck's sarcoid*. Seven of the patients had cutaneous manifestations of the disease, while this localization was not demonstrable in 3 of the patients. The papule caused by the antigen was excised and examined histologically in 9 of the patients at various times (weeks, months and years) after injection.

Table I is a compilation of the results of the most important examinations in 7 patients with cutaneous manifestations of Boeck's sarcoid (as well as a number of other localizations of the disease).

*Case 1.* Lars Aa, a 48 year old farmer has in the course of the past 8 years developed slowly growing, brownish-red, cutaneous-subcutaneous infiltrations of the face. At the time of the first examination at the Dermatological Clinic he had along the right cheek bone and forward on the right cheek a 3 × 8 cm flat infiltration and similar infiltrations, about 2 × 2 cm, in the right eyebrow and on the left cheek. Clinical examination of the patient revealed nothing further.

Roentgenogram of the *lungs* showed: Doubtful hilus adenitis on the left side. *Hands and feet*: Small cyst-like clearings in the distal end of the ulna on both sides and in the left os lunatum, otherwise negative findings.

Wa. R. —, Pirquet —, Mantoux with 1/10 mg tuberculin —.

*Kveim's reaction*: About 1 week after the injection, a brownish-red nodule began to develop, which after 3 weeks had a diameter of 5 mm. This remained unchanged for some time and after 6 weeks the nodule was excised and examined histologically with the following result: Small infiltrations in the corium composed of epithelioid cells with a moderate border of lymphocytes. Isolated giant cells of Langhans' type.

*Resumé*: This is a typical case of Boeck's sarcoid with pronounced cutaneous manifestation. Kveim's reaction is positive since a millet seed sized, brownish-red papule appeared at the point of injection in the course of a few weeks. This papule was excised after 6 weeks and histologically showed a construction similar to that found in spontaneous Boeck's sarcoid infiltrations.

*Case 2*. Petter B. is a 40 year old storekeeper who in the course of 3—4 years has developed multiple cutaneous-subcutaneous nodules of the face, back, buttocks, upper arms and thighs. Examination revealed large, swollen glands in the neck, axillae and groin, but there were no other pathological findings.

Roentgenogram of the *lungs*: Enlarged glands in the left hilus. Parenchym congestion in left lung. Prominence of the pulmonary arch. Slightly enlarged vessels in the right hilus. *Hands and feet*: Negative.

Wa. R. —, Pirquet —, Mantoux 1/10 mg —. Biopsy from the skin and swollen gland showed a histological picture typical for Boeck's sarcoid.

*Kveim's reaction*: In the course of the first week a 3 mm brown spot developed which became infiltrated in the course of a week. After 18 days the papule had a diameter of 3 mm, the color was paler. A new antigen was injected which after 1 week caused a papule of 5 mm's diameter, and this remained almost unchanged for 5 weeks when it was excised. Histological examination showed: In a limited area of the corium there are small masses of epithelioid cells and some giant cells of Langhans' type. No necrosis. In the peripheral parts a diffuse infiltration of lymphocytes.

*Resumé*: Kveim's reaction is positive in a 40 year old man with a typical clinical picture of Boeck's sarcoid. After a few weeks a distinct papule develops at the point of injection and this papule is histologically examined after 5 weeks. Its construction is similar to that found in spontaneous Boeck's sarcoid infiltrations.

*Case 3*. Borgh. B. is a 27 year old typist who in the course of 1 ½ year had developed an affection of the skin and bones localized to several fingers. The left forefinger is brownish in color and thickened in the

Table 1. *Kveim's reaction in patients with Boeck's sarcoid*

Case no.	Name	Age	Localization of the cutaneous manifestations	Roentgenfindings	
				Lungs	Bones
1	Lars Å.	48	Face	Doubtful hilus adenitis	Cystic transparencies
2	Peter B.	40	Face, nates, extremities	Swollen glands in left hilus. Parenchym congestion in left lung.	Negative
3	Borghild B.	27	Fingers	Negative	Osteolytic process in several finger.
4	Hans R.	55	Left ear	Bilateral hilus adenitis	Negative.
5	Ingeborg T.	36	Face	Negative.	Negative.
6	Emma B.	37	Right leg	Bilateral hilus adenitis. Infiltratio pulm. dext.	Not examined.
7	Evelyn B.	28	Left shoulder and both upper arms.	Negative.	Not examined.

<sup>1</sup> 15 mm infiltration and 20 mm erythema.

who also have cutaneous manifestation of the disease.

Pirquet's reaction	Mantoux 1/10 mg tuberculin	Kveim's reaction	
		Clinical development	Histological examination of extirpated papule
÷	÷	After 1 week a papule which after 3 weeks had a diameter of 5 mm.	Extirpated after 6 weeks: In corium infiltrations of epithelioid cells surrounded by lymphocytes. Some giant cells of Langhans' type.
÷	÷	A small papule in the course of the 1st week. Diameter 3 mm after 18 days.	Extirpated after 5 weeks: In corium small masses of epithelioid cells, some giant cells of Langhans' type. Peripheral diffuse lymphocyte infiltration.
÷	15/20 <sup>1</sup>	After 1 week a brownish-red papule with 6 mm diam. Remained almost unchanged for 10 weeks.	Extirpated after 10 weeks: In corium well defined masses of epithelioid cells surrounded by lymphocytes. No giant cells but tendency to formation of monstrous epithelioid cells.
÷	÷	After 2 weeks a brownish-red papule of 4 mm diam.	Not examined.
÷	÷	After a few days a brownish-red papule of 3 mm diam. It grew slowly and 6 weeks later was 5 mm in diam.	Extirpated after 12 months: In corium a mass of epithelioid cells surrounded by lymphocytes. No giant cells, no necroses.
÷	÷	No reaction the first 2 weeks. After 5 weeks a papule with 5 mm diam. This papule was unchanged 14 months later.	Extirpated after 14 months: In corium and near the hair follicles masses of epithelioid cells. Lymphocyte infiltration. No necroses, no giant cells.
÷	÷	Neg. reaction the first 6 weeks. 8 ½ months later a papule of 3 mm diam. 12 months after injection the papule was 5 mm in diam.	Extirpated after 14 months: In corium a mass of epithelioid cells with small, central necrosis and surrounded by lymphocytes. No giant cells.

region of the terminal phalangeal bone. The nail is atrophic, partly sloughed off, the remaining parts are discolored and flaky. The skin has a comparatively soft consistency, especially because the terminal phalangeal bone is partly destroyed by ulceration (cf. roentgen). On anæmization with a glass spatula numerous miliary foci can be seen in the brownish skin. Similar skin changes are found in the left ring finger and the right little finger. The latter is misshapen in the form of a spool corresponding to the interphalangeal joints, and the skin is brownish, taut and shiny, of a soft consistency with abundant miliary foci on pressure with glass.

The clinical examination revealed no other pathological findings.

*Roentgenogram: Lungs:* negative. *Hands:* osteolytic processes in the fingers, especially in the fingers which show the clinical changes described above. *Feet:* negative.

Histological examination of the infiltrations of the fingers and the extirpated terminal phalanx of the left forefinger: The corium is full of numerous masses of epithelioid cells surrounded by lymphocytes. In the central parts there is limited necrosis. No giant cells.

The tissue was inoculated into a guinea-pig but with negative result. Direct cultivation of tb. according to the sulphuric acid method also gave negative results.

Wa.R. —, Pirquet — (twice), Mantoux with  $\frac{1}{10}$  mg tuberculin gave a positive reaction of 15/20 after 24 hours (15 mm infiltration, 20 mm rubor), after 48 hours 15/25 and after 72 hours 10/20.

*Kveim's reaction:* After little more than a week a distinct brownish-red papule with a diameter of 5—7 mm developed. This remained almost unchanged for 10 weeks, when it was excised. The histological examination showed well defined masses of epithelioid cells in the corium surrounded by a small border of lymphocytes. No necrosis. No typical giant cells but a tendency to the formation of monstrous epithelioid cells.

*Resumé:* In a 27 year old woman inflammatory infiltrations developed in the course of 1  $\frac{1}{2}$  years in several fingers with destructive processes of the finger bones. According to the clinical examination the choice of diagnosis is between a tuberculous process and Boeck's sarcoid. The roentgenological findings with osteolytic processes in the phalanges of the fingers indicate the possibility of a tuberculous process with a picture in this case very similar to spina ventosa tuberculosa. Moreover the patient had a positive Mantoux reaction with  $\frac{1}{10}$  mg tuberculin, while Pirquet's reaction was negative. The negative inoculation of a guinea-pig (and the negative attempts at tb. cultivation) speak against the assumption of a tuberculous process. In addition *Kveim's reaction* is positive. Similar clinical pictures of Boeck's sarcoid have also been observed previously at the clinic and have also been

described from other clinics, e. g. in the report of the Strassburger Congress in 1934.

In this case also the extirpated papule, Kveim's reaction, showed the same composition as found in Boeck's sarcoid.

*Case 4.* Hans R., a 55 year old manager, has in the course of several years developed a skin affection localized to the left ear lobe and adjacent areas of the external ear. The skin is brownish-red, thickened, with numerous milia and teleangiectases. The consistency is comparatively soft. On pressure with glass, numerous miliary foci can be seen. The physical examination of the patient revealed no other pathological findings.

*Roentgen: lungs:* bilateral hilus adenitis. *Hands and feet:* negative. *Wa.R. —, Pirquet —, Mantoux with  $\frac{1}{10}$  mg tuberculin:* neg.

*Kveim's reaction:* After 2 weeks a brownish-red grain-sized papule, 4 mm in diameter. (The papule was not examined histologically.)

*Resumé:* In a 55 year old man with a typical picture of Boeck's sarcoid localized to the left ear, Kveim's reaction is positive with a distinct grain-sized papule after 2 weeks.

*Case 5.* The patient is a 36 year old woman (Ingeborg T.) who in the course of 6 months has developed several nodules in the face. Examination in the out patient department revealed a bean-sized, bluish-red infiltration on the right cheek, and a pea-sized infiltration on the right angulus mandibulae. Palpable glands in the neck, under the mandibulae and in the axillae. Clinical examination revealed no other pathological findings.

A biopsy was made of one of the infiltrations and histological examination revealed a composition typical for Boeck's sarcoid: In the corium some sharply limited, some confluent infiltrations consisting of epithelioid cells surrounded by borders of lymphocytes. Isolated giant cells of Langhans' type. No necrosis. Tissue was cultivated according to the sulphuric acid method for tb, and tissue was also inoculated into a guinea-pig with negative results.

*Roentgen: lungs:* negative. *Hands and feet:* negative.

*Wa.R. —, Pirquet —, Mantoux with  $\frac{1}{10}$  mg tuberculin:* neg.

*Kveim's reaction:* After a few days there appeared a small papule with a diameter of 3 mm. It grew slowly and after 6 weeks had a diameter of 5 mm. On control examination 1 year later there was still a distinct papule with a diameter of 4 mm. *Excision:* Histological examination revealed a nodule in the corium consisting of epithelioid cells surrounded by lymphocytes. No giant cells, no necrosis.

*Resumé:* The patient is a 36 year old woman with typical cutaneous manifestations of Boeck's sarcoid. Kveim's reaction is positive after a few days, and a distinct papule at the point of injection persists almost unchanged for a year, after which it is examined histologically. Specific chronic inflammatory changes

are demonstrated, changes similar to those found in Boeck's sarcoid.

*Case 6.* The patient is a 37 year old seamstress (Emma B.) who was sent to the out patient department for an infiltration on the right leg, which she had had for about 5 months. Just above the malleolus int. on the right leg was a limited infiltration of brownish-red color, flat and not sharply defined, about the size of a child's hand. The surface is smooth with no ulcerations or scars. Consistency hard and elastic. The patient claims slight sensitivity to pressure. Ordinary clinical examination revealed no further pathological findings.

*Roentgen: lungs:* bilateral hilus adenitis and a bean-sized infiltration beyond and below the right hilus.

Wa.R. —, Pirquet —, Mantoux with  $\frac{1}{10}$  mg tuberculin: neg.

*Kveim's reaction:* No reaction during the first 2 weeks. Control after 5 weeks revealed a brownish-red papule with a diameter of 5 mm. The patient did not show up for control and did not return until 14 months after the injection of the antigen. There was still a brownish nodule in the skin with a diameter of about 5 mm. This nodule was extirpated and examined histologically with the following result: In the corium and the vicinity of the hair follicles there are numerous, sometimes isolated, sometimes confluent masses of epithelioid cells, which are sometimes penetrated and sometimes surrounded by abundant lymphocytes. No certain necrosis nor giant cells.

*Resumé:* The patient is a 37 year old woman who in the course of 5 months has developed an infiltration on the inside of the right lower leg which probably should be interpreted as a manifestation of Boeck's sarcoid. (The infiltration was not examined histologically as in all the other cases.) Moreover the patient has a lung affection which both clinically and roentgenologically points in the direction of Boeck's sarcoid. Pirquet's and Mantoux' reactions are repeatedly negative. In this patient *Kveim's reaction* is positive, as a distinct papule developed at the point of injection after a few weeks. This papule persisted almost unchanged for over a year and *after 14 months was extirpated*. The histological examination of the papule revealed changes of a chronic, inflammatory nature.

*Case 7.* The patient is a 28 year old woman (Evelyn B.) who in the course of several years has developed several bluish-red infiltrations in the skin. On the left shoulder and both upper arms, especially on the flexor surfaces, are several distinctly infiltrated, cutaneous-subcutaneous nodules in the skin, up to walnut size, not sharply limited. The nodules are not sensitive. On pressure with glass a number of yellowish, miliary foci are

visible. She has some palpable, insensitive glands in the neck. The ordinary clinical examination reveals no other pathological findings.

*Roentgen:* lungs: negative.

*Cytological blood examination:* normal findings.

*Histological examination of the infiltrations in the skin:* In the upper layers of the skin there are small, perivascular lymphocyte masses. Deeper in the corium and down to the limit of the subcutis there are numerous, well defined nodules which are occasionally confluent. These consist for the most part of epithelioid cells and in many of them there is a central necrosis. In the peripheral areas, also diffusely among the epithelioid cells, there is a moderate infiltration of lymphocytes. There are no certain giant cells.

*Wa.R. —, Pirquet —, Mantoux with  $\frac{1}{10}$  mg tuberculin:* neg.

*Kveim's reaction:* (The patient lives about 100 km from Oslo and came to the out patient department for examination.) The reaction was controlled after 2 weeks when there was a very slight infiltration and the reaction was recorded «trace?». After another 2 weeks there was still no change in the reaction, nor after 6 weeks. The patient did not return until 8½ months after the injection of the antigen. At the point of injection there was now a small brownish papule 3 mm in diameter. The patient was again examined 1 year after the injection of the antigen. The papule had grown and was now 5 mm in diameter. It remained unchanged for another 2 months and was then extirpated. The histological examination gave the following results: In the corium there is a mass of epithelioid cells. There is a small, central necrosis. Moderate infiltration of lymphocytes. No certain giant cells.

*Resumé:* A 28 year old woman has for several years had walnut-sized cutaneous-subcutaneous infiltrations in the skin of the shoulder and upper arms. Cytological blood examination and roentgen examination of the lungs revealed no pathological changes. *Wa.R.* negative as well as tuberculin reactions (performed several times). The clinical diagnosis was Boeck's sarcoid as it was possible to exclude tuberculosis, lymphogranulomatosis, leucæmia, neoplas-mata, syphilis and several other less common diseases which entered into the differential diagnostic considerations. The histological picture of an extirpated nodule from the skin also spoke in favor of Boeck's sarcoid. Kveim's reaction was carried out but gave negative results during the first 6 weeks. After more than 8 months we had the opportunity to examine the patient again and at that time there was a small papule at the point of injection. This papule grew slowly and was 5 mm in diameter when it was extirpated 14 months after the antigen was injected. The histological examination of the papule revealed the same structure demonstrated previously in patients with Boeck's sarcoid.



Table 2. *Kveim's reaction in patients with Boeck's sarcoid,*

Case No.	Name	Age	Most important localization of the disease	Roentgen findings	
				Lungs	Bones
8	Gudrun H.	40	General swollen glands	Parenchym congestion basally in right lung.	Negative
9	Lorang H.	33	Uveitis, general swollen glands.	Bilateral hilus adenitis. Lung congestion in small spots.	Not examined.
10	Dagny K.	21	Lungs.	Parenchym congestion, diffuse in both lungs.	Not examined.

In 7 patients described above, all of whom presented the clinical picture of Boeck's sarcoid with cutaneous manifestations, Kveim's reaction has been carried out. The antigen has caused a positive reaction from 1—4 weeks after injection in most cases. In 2 patients who did not present the classical clinical picture of Boeck's sarcoid (Cases 6 and 7) the reaction was not positive until several weeks later, in the last case more than 6 weeks after the injection of the antigen in the skin. In both of these patients the reaction remained positive for more than 1 year after the injection of the antigen. In both cases the papule was examined histologically and with the same result, as tissue was demonstrated with a histological structure very similar to that found in spontaneous sarcoid manifestations.

The result of Kveim's reaction has also been investigated in 3 patients with Boeck's sarcoid without demonstrable cutaneous manifestations of the disease (Table 2).

but without demonstrable cutaneous manifestations of the disease.

Pirquet's reaction	Mantoux 1/10 mg tuberculin	Kveim's reaction	
		Clinical development	Histological examination of extirpated papule
÷	10/15 <sup>1</sup>	After 1 week a distinct papule, diam. 9 mm. Unchanged after 2 weeks.	Extirpated after 2 weeks: In corium small infiltrations consisting of fibroblasts (epithelioid cells?) and giant cells of the foreign body type. Diffuse infiltration of lymphocytes, fibroblasts and some plasma cells.
÷		After a few days a distinct papule, 3 mm diameter. Unchanged for 6 weeks.	Extirpated after 6 weeks: In the upper layer of the corium an elongated mass of epithelioid cells with some giant cells. Some lymphocytes and fibroblasts. No necrosis.
÷	÷	After 1 week a papule, 4 mm in diameter.	Extirpated after 6 weeks: In corium masses of epithelioid cells surrounded by lymphocytes. Some giant cells of the foreign body type.

<sup>1</sup> 10 mm infiltration and 15 mm erythema.

*Case 8.* The patient is a 40 year old woman (Gudrun II.) who was sent to the Out Patient Dept. The patient stated that she had 2 years previously been treated in hospital for «swollen glands» in the neck, the axillae and groins. At that time a gland was extirpated for histological examination. It was comprised of granulation tissue containing masses of epithelioid cells and large giant cells of Langhans' type. The histological diagnosis was «Boeck's sarcoid? tuberculosis?» Pirquet's reaction was repeatedly negative. Examination at the Dermatological Out Patient Department of the Rikshospital revealed no cutaneous manifestations (except pityriasis versicolor). In the neck, axillae and groin were hard, palpable, insensitive glands.

*Roentgen: lungs:* Parenchym congestion basally in right lung. *Hands and feet:* negative.

*Wa.R. —, Pirquet —, Mantoux with 1/10 mg tuberculin* showed after 24 hrs 5/5, after 48 hrs 10/15 (control with broth dilution 5/5).

*Kveim's reaction:* After 1 week there was a papule with a diameter of 9 mm and this was unchanged at the next control a week later. The 2 week old papule was extirpated and the histological examination gave the fol-

lowing result: In the corium there were small infiltrations consisting of fibroblasts (epithelioid cells?) and these infiltrations were partly bordered by giant cells of the foreign body type. Moreover there was a rather diffuse infiltration of mostly lymphocytes, fibroblasts and some plasma cells.

*Resumé:* In a 40 year old woman who for several years has had general swollen glands, which contain a granulation tissue which has a structure agreeing with the diagnosis of Boeck's sarcoid there is a negative Pirquet and a weak positive Mantoux' reaction. Kveim's reaction is positive after a week and after 2 weeks the papule is extirpated and examined histologically. It consists of granulation tissue described above in detail.

*Case 9.* The patient is a 33 year old man (Lorang H.) who was sent to the Dermatological Out Patient Dept. from the Ophthalmological Dept. where he was being treated for uveitis. He had no skin symptoms. In the neck, axillae and groin there were slightly enlarged glands.

*Roentgen: lungs:* Bilateral hilus adenitis, congestion of the lungs in small spots.

Wa.R. —, Pirquet —.

*Kveim's reaction:* After a few days a distinct papule of 3 mm diameter appeared and remained unchanged for 6 weeks when it was extirpated. The histological examination of the papule revealed: In the upper layers of the corium an elongated mass of cells with some epithelioid cells, numerous fibroblasts and some giant cells with peripheral nuclei. A few lymphocytes among the fibroblasts but no necrosis.

*Resumé:* A 33 year old man has uveitis, general swollen glands and a lung roentgenogram which suggests Boeck's sarcoid. This diagnosis becomes even more likely on the demonstration of negative Wa.R., negative Pirquet and Mantoux. Kveim's reaction is positive and the papule developed is extirpated after 6 weeks and examined histologically. A granulation tissue is found with a structure very similar to that found in spontaneous sarcoid nodules.

*Case 10.* The patient is a 21 year old woman (Dagny K.) who was sent to the Out Patient Dept. from Med. Dept. where she was being treated under the diagnosis: Infiltratio pulm. (*Boeck's sarcoid*). She had had a «cold» for a year with running nose and coughing. At the Medical Dept. roentgen examination had revealed diffuse parenchym congestion of both lungs. Repeated investigations were made for tb. in her expectoration but with negative results.

Wa.R. —, Pirquet —, Mantoux with  $\frac{1}{10}$  mg tuberculin: neg.

*Kveim's reaction:* After 1 week there appeared a brownish red papule with a diameter of 4 mm. It remained almost unchanged and after 8 weeks had a diameter of 5 mm. The papule was extirpated and examined

histologically with the following result: In the corium were several masses of epithelioid cells bordered by lymphocytes. There were also some giant cells of the foreign body type.

*Resumé:* A 21 year old woman has suffered for a year from symptoms of a lung affection. Diffuse parenchym congestion was demonstrated in both lungs. All attempts to demonstrate tb. in the sputum were negative. Pirquet —, Mantoux —. *Kveim's reaction* was positive and the papule produced was examined histologically after 8 weeks. This revealed a granulation tissue of a chronic specific nature.

In 3 patients with Boeck's sarcoid but without demonstrable cutaneous manifestations of the disease, Kveim's reaction was found to be positive and in all the cases the papule produced was examined histologically from 2—8 weeks after the antigen was injected into the skin. In these cases also a granulation tissue of a chronic specific nature was demonstrated with a tissue structure similar to that found in spontaneous sarcoid nodules.

These results of the continued investigations on Kveim's reaction fully support the interpretation which A. Kveim presents in his above mentioned preliminary paper, that we are dealing with an *allergic cutaneous reaction which is specific for Boeck's sarcoid*.

The antigen used is, as mentioned above, a suspension of «sarcoid» tissue. We have produced antigen from nodules in the skin, from a finger tip (with bone tissue) which was penetrated by «sarcoid tissue» (from Case 3) and from swollen glands. It has been found that gland material has given the most active antigens. An antigen made from an extirpated gland from Case 2 gave a positive but slight reaction in the same patient while the same antigen caused much stronger reactions in other patients. A Berkefeld filtrate of a tissue suspension has also been tested in order to determine whether the action of the antigen is dependent upon the presence of corpuscular elements. These investigations are not yet concluded, but for the present seem to be without result, possibly because the tissue suspension must be diluted still more in order to carry out the necessary filtration.

The antigens we have used have been stored with good results. Kept in a refrigerator they have been just as effective after several months.

Many difficulties are involved in obtaining sufficient quanti-

ties of antigen. Patients with Boeck's sarcoid who have swollen glands suitable for extirpation are not so numerous, nor are the patients always willing to allow extirpation. The extirpated gland must be examined microscopically in order to determine that it is really composed of »sarcoid» tissue. Part of the gland must also be used for cultivation of tb., and part of it for guinea-pig inoculation. The finished antigen can only be used when the ordinary sterility controls are in order, and after sufficient time has elapsed to determine that cultivation of tb. and the guinea-pig inoculation are negative. The production of the antigen is therefore difficult except in departments which have a reasonable number of patients with Boeck's sarcoid and where there is also opportunity to work in cooperation with a bacteriological laboratory.

It is peculiar that the cutaneous reaction produced in patients with Boeck's sarcoid after intradermal injection of 0.1—0.2 cm<sup>3</sup> of antigen appears first after several days, in some cases only after several weeks. However in most cases a positive reaction will manifest itself in the course of a week. But the papule produced will usually increase in extent during the subsequent weeks and in most cases reach their maximum development after 4—8 weeks. They usually persist for several months and can disappear gradually spontaneously. In 2 of the cases the positive reaction appeared very late. In Case 6 the reaction was negative 2 weeks after the injection but was positive when controlled 3 weeks later. The reaction thus manifested itself as positive between the 2nd and 5th week after the injection of the antigen. In Case 7 the reaction was negative for the first 6 weeks. Unfortunately the patient was not controlled again until 8 months after the injection, and at that time a distinct papule was seen. These observations demonstrate the necessity of controlling the point where the antigen has been injected not only for many weeks, but for several months before the nature of the reaction can be definitely determined.

It is a very remarkable phenomenon that the papule which develops in patients with Boeck's sarcoid after the injection of the antigen, has a histologic structure which in some cases is completely analogous with the structure of spontaneous sarcoid infiltrations. Kveim has pointed out this phenomenon in his first publication. In 9 of the cases referred here the papule was ex-

amined histologically and in all the cases a granulation tissue was demonstrated with epithelioid cells, lymphocytes and usually also giant cells which in 3 cases were of Langhans' type, and in 2 cases of the foreign body type. The papules examined were of varying ages, so that a more detailed analysis of the histological findings in this material is not likely to give any particular results. The results of the histological examinations of papules produced by an antigen which has been injected 14 months previously (Cases 6 and 7) are of special interest. In both of these cases there were epithelioid cell masses with lymphocyte borders but no giant cells.

The demonstration of a new specific cutaneous reaction for Boeck's sarcoid will be of significance for the diagnosis of this disease, especially in cases where the patient has *no* typical cutaneous manifestations of the disease. Where the patient has *cutaneous manifestations*, the clinical examination supported by microscopical and cultural examinations of extirpated tissue, together with the result of the tuberculin tests, will give a reliable diagnosis. But where the patient has only «internal» localizations of the disease, the result of Kveim's reaction may be of decisive importance for the diagnosis.

The new reaction is also of interest in connection with the discussion of the etiology of Boeck's sarcoid. The fact that Kveim's reaction is positive only in cases of Boeck's sarcoid and not in e. g. lupus vulgaris or tuberculids, indicates decidedly that Boeck's disease must be regarded as a disease *sui generis*. Kveim's reaction is an important argument for this assumption. It is an entirely different matter that a striking tuberculin anergi in Boeck's sarcoid shows that the disease probably has some relation to tuberculosis. In future discussions of the etiology of Boeck's sarcoid, Kveim's reaction must be taken into consideration. Further studies of allergic reactions in Boeck's sarcoid will most certainly contribute still more to the elucidation of the etiology of this strange disease.

### Summary.

With reference to A. Kveim's report in N. M. 1941: 9: 169 an account is given of the results of investigations with Kveim's reaction in 10 patients with Boeck's sarcoid. In all cases Kveim's

reaction was positive. The antigen, which is produced from »sarcoid» tissue from lymph glands, is injected intracutaneously in quantities of 0.1—0.2 cm<sup>3</sup>. After a few days a papule appears which grows slowly during the subsequent weeks. In a few cases the papule did not develop until several weeks after the injection. In 9 cases the positive reaction (papule) was extirpated and examined histologically. In all cases it was found to consist of granulation tissue containing epithelioid cells surrounded by lymphocytes. Giant cells of Langhans' type were also found several times. The histological picture was very similar to the microscopical structure of sarcoid tissue. In 2 cases the papule was extirpated over a year after the injection of the antigen and in both these cases a granulation tissue of chronic specific nature was demonstrated.

The diagnostic significance of the reaction is discussed. In 3 of the patients referred here the patients had no *cutaneous* manifestations of the disease. In such cases, with only »internal» localizations of Boeck's sarcoid, Kveim's reaction will be of great diagnostic significance.

The demonstration of a specific cutaneous reaction in Boeck's sarcoid also supports the interpretation that this is a disease *sui generis*, which should not be interpreted as a form of tuberculosis.

### Zusammenfassung.

Indem verwiesen wird auf die Mitteilung von A. Kveim in *Nordisk Medicin* 1941: 9: 169, wird das Ergebnis mitgeteilt einer Untersuchung der Kveimschen Reaktion bei 10 Patienten mit Boeckschem Sarkoid. In sämtlichen Fällen war die Kveimsche Reaktion positiv. Das Antigen, das aus »Sarkoid»-Gewebe aus einem Lymphknoten gewonnen war, wurde intracutan eingespritzt in Mengen von 0.1—0.2 ml. Nach wenigen Tagen bildete sich eine Papel, die im Laufe der ersten Wochen langsam wuchs. In einzelnen Fällen trat die Papel erst mehrere Wochen nach dem Setzen des Antigens auf. In 9 Fällen wurde die positive Reaktion (Papel) exzidiert und histologisch untersucht. In sämtlichen Fällen fand man ein Granulationsgewebe, bestehend aus epithelioiden Zellen, umgeben von Lymphocyten. Mehrfach wurden auch

Riesenzellen vom Langhanschen Typus aufgefunden. Das histologische Bild weist grosse Ähnlichkeit auf mit dem mikroskopischen Bau des »Sarkoid«-Gewebes. In 2 Fällen wurde die Papel mehr als ein Jahr nach dem Setzen des Antigens ausgeschnitten; in beiden Fällen wurde ein Granulationsgewebe chronisch spezifischer Natur vorgefunden.

Die diagnostische Bedeutung der Reaktion wird besprochen. In 3 der mitgeteilten Fälle hatten die Kranken keine *cutanen* Manifestationen der Krankheit. In solchen Fällen, wo das Boeck'sche Sarkoid ausschliesslich »intern« lokalisiert ist, kommt der Kveimschen Reaktion grosse diagnostische Bedeutung zu.

Der Nachweis einer spezifischen *cutanen* Reaktion bei Boeck'schem Sarkoid bildet ferner eine Stütze der Auffassung, dass man es hier mit einer Krankheit *sui generis* zu tun hat und nicht mit einer besonderen Form von Tuberkulose.

### Résumé.

En se référant au rapport préliminaire de A. Kveim, publié dans *Nordisk Medicin*, 1941, 9, p. 169, on rapporte ici les résultats de l'examen de la réaction de Kveim chez 10 malades atteints du sarcoïde de Boeck. Dans toutes les observations, la réaction de Kveim était positive. Avec 0.1—0.2 cm<sup>3</sup> d'antigène qui a été préparé d'un tissu »sarcoïde« d'un ganglion lymphatique, il a été fait une injection intra-cutanée. Après quelques jours, il s'est formé une papule qui a augmenté lentement de volume au cours des premières semaines. Dans quelques cas, la papule s'est présentée seulement plusieurs semaines après l'injection à l'antigène. Dans 9 cas, la papule a été extirpée et examinée histologiquement. La biopsie a, dans tous les cas, montré une infiltration dermique composée de cellules épithéloïdes entourées de lymphocytes. Plusieurs fois, on a observé aussi des cellules géantes du type Langhans. Le tableau histologique présentait une grande ressemblance avec celui du tissu »sarcoïde«. Dans 2 cas, la papule a été extirpée plus d'un an après l'injection de l'antigène, et, les deux fois, l'examen histologique a révélé un infiltrat cellulaire de même caractère spécifique.

L'importance diagnostique de la réaction est mentionnée. Dans 3 des observations référées ici, les malades n'avaient aucune



manifestation *cutanée* de la maladie. Dans de semblables cas de localisation exclusivement »interne» du sarcoïde de Boeck, la réaction de Kveim aura une grande importance diagnostique.

La démonstration d'une réaction cutanée spécifique dans le sarcoïde de Boeck donne aussi appui à cette conception, qu'on se trouve, ici en présence d'une maladie *sui generis* qui ne doit pas être considérée comme une forme spéciale de la tuberculose.

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## Myoporphyrria

by

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In very rare cases one has been able to observe an abnormal secretion of porphyrin in the urine in the progress of inflammatory and degenerative changes of the striated muscular tissue. In contrast with the opinion that in most cases of abnormal porphyrinuria the blood may be considered as starting-material, in these very rare cases the muscle-pigment should be the source of the porphyrin which has been formed and secreted. One should however bear in mind that clinically myoporphyrria is very difficult to distinguish from the other porphyrinurias. Yet this is a very important question in the criticism of the study of the porphyrrias. It is not impossible that several cases of porphyrria which have been described in the literature of the last years must be conceived as myoporphyrrias. We know so little yet of the biological problems which are connected with the muscle-pigment. Both about its building-up and demolition we know still very little. Important questions, whether in its demolition also bilirubin, urobilin or another substance, *i.e.* the urochrome from the urine is formed, still wait for an answer. Certainly it is remarkable that with all the studies about the destiny of hemoglobin one is practically not interested in myoglobin, and virtually takes little or no account of it in its contemplations.

An abnormal mobilization of muscle-pigment and its secretion in the urine is known to us by the name of »myoglobinuria». From

a few examinations it has been appeared that with marchhemoglobinuria in reality one has to deal with a myoglobin-secretion. Also the Haf-disease described in Germany is accompanied by a myoglobinuria. With horses the paroxysmal myoglobinuria with heavy muscular injury, and paralysis of the hindlegs, is a well-known symptom. Now it is not easy to distinguish hemoglobin from myoglobin. Spectroscopically there is only an extremely small distinction which can only be fixed by spectrographical determination. Presumably the difference is to be attributed to a somewhat different composition of the globin-component.

We know from laboratory-research that both under septic and aseptic conditions large quantities of porphyrin are formed from myoglobin after death. About the question whether such a thing also takes place in human pathology, very few communications are found. Only a few cases of porphyria have been described, of which the investigators thought that those porphyrins did not proceed from the blood, but from the muscle-pigment.

We will communicate here a case of which we may assume that we have to deal with a myoporphyria.

Patient van B. is a still young man of 28 years, field-labourer. Two weeks before admission started with stomach-ache. This appeared in fits, drew up from under the navel, and was attended with vomiting. He describes it as typical colic-pains. About 4 years ago he had similar pains during a short time. These were ascribed to the stomach. His bad teeth were then removed, and replaced by a prothesis. Between the painattacks he has now a feeling of flatulence. These two weeks he has been strongly obstipated. His appetite has remained good. He has also some cramp in urinating, and it has struck him that he often voids but small portions. When he has these vesicular cramps, the urine is of a somewhat darker colour, but again normally clear between the attacks. In particular parts of arms and legs, especially in the muscular part, he has also had cramps. When he has these, the muscles are painful, when he touches them, and he cannot exert any strength with them. A few hours later, when the cramps are past, the painfulness has also given way, and he disposes again of proper strength according to what he says himself. Yet he has become thinner and weaker in these few weeks, and complains

about a general impotence. Already through the family-anamnesis the diagnosis became probable, for six years ago his brother was in hospital with fairly the same symptoms. The diagnosis was then made on acute porphyria. He left the hospital cured, has had slight cramps since occasionally, but has for the rest always continued to feel well, and has been able to perform his work well. Also with our patient a porphyria appeared to be the case. In the urine some copro- and large quantities of uroporphyrin were found. Beside those a fair quantity of urobilin was present in the urine. No anemia existed, the full 100% of hemoglobin was found. Number of red bloodcells 5,170,000. There were no symptoms which pointed to a powerful new formation, neither in the peripheral blood nor in the fluid obtained by puncture of the bone-marrow. The bilirubingrade of the serum amounted to 0,4 E., indirect. At the extremities all reflexes were present, though not all equally brisk. Thus the right patella-reflex was somewhat lower than the left, but the Achilles tendon reflex was equal on both sides. The sensibility was undisturbed.

After daily intravenous administration of large quantities of calciumgluconate, the giving of proper doses of natriumcarbonate, and pernaemon, the abdominal symptoms gradually decreased in the course of about ten days, the spastic obstipation disappeared. On the other hand more and more cramps occurred. At a fairly quick pace a very distinct atrophy of the muscles of pelvis and shoulder-girdle developed itself, but also of trunk and the greater part of the extremities. The tensors of fore-arms and hands, especially the left fore-arm, were more atrophic than the flexors. The sensibility remained perfectly unimpaired. The peripheral reflexes became low, but were maintained. Only the cremasteric reflexes were no longer to be stimulated. The patient was only capable of a few movements, and then exclusively with the flexors. This applied both to arms and to legs. There was no definite developing of the symptoms from the lower part of the body to higher regions. The left fore-arm was thoroughly affected first of all, then followed the muscles of the pelvis, and both upper legs, after that the left shoulder, then the right shoulder, right foreleg, left fore-arm and left fore-leg. Of a paralysis according to the Landry-type be hardly spoken. It is remarkable that jugular and cervical muscles have not joined in it. On the cerebral nerves we found no deviations,

there were no bulbar symptoms, the diaphragm continued to function normally. More than four weeks after the admission the process did not proceed any further, and gradually the patient recovered. During these four weeks the kidneys continued to secrete daily large quantities of porphyrin. Exactly 29 days after admission no porphyrin was to be found any more in the urine. This cessation of the porphyrin secretion was rather sudden. Till three days before, daily still large quantities, in three days a fall to nothing. During the period of porphyrin-secretion we have watched the creatinin-secretion a few times. This was fairly considerable. How great it has been totally, we cannot say; it was rather variable. On the last day, when porphyrin could still be indicated, the creatinin secretion amounted still to 550 mgrs. On the next day there were still few milligrammes, and three days later perfectly negative. Simultaneously with the cessation of the creatinin-secretion no more porphyrin could be shown.

During this month, when daily large quantities of porphyrin were secreted, the blood-picture remained practically unchanged. On the day, when the porphyrin had disappeared from the urine, the number of red bloodcells amounted to 5,200,000.

The urine was generally fairly clearly voided, but assumed, when standing over, an intensive dark colour, almost black. It is not my intention to go further into the properties of the porphyrins found with this patient in this communication. I hope to describe still further the chemical curiosities attending them. Only I will point out here that this brownish, black pigment of the urine must fairly certainly proceed from the blood- or muscle-pigment; presumably from the globin-component. The secretion of this pigment, so little known yet did not end so abruptly as porphyrin, but was still to be found about a week in ever diminishing quantities.

So we have here to do with a case of familiar porphyria which we think we should regard as the result of a disturbance in the metabolism of the muscle-pigment, and that we must speak of myoporphyria. If such a thing has also been the case with his brother, may be probable, though at the time this possibility was not thought of at the investigation. The disease of this brother progressed much lighter, lasted shorter, and it did not come to heavy paralysis. With him, too, no trace of anemia appeared, all

reflexes were maintained, and no disturbances of sensibility were found.

The most important points, wherefore we think we may conclude in this case to the existence of a myoporphyrinuria, are:

Firstly: the failing of anemia, and the absence of any symptom which points to a powerful regenerative manufacture of new red bloodcorpuscles.

Secondly: the simultaneously appearing strong muscular atrophy without there being other symptoms which made the diagnoses of a polyneuritis acceptable. Also the process was attended with pains which were more localised in the muscles than in the course of the nerve-stems. The atrophies also appeared in very divergent muscle-groups without there being any connection with the nerve attending to them. Of muscle-groups which belong to one and the same nerve, some muscles were affected, whereas others were not.

Thirdly: the large quantity of creatinin which was secreted during the course of the disease with the urine, while this secretion ceased simultaneously with the termination of the porphyrinuria. In literature we only find the following cases:

1. Vanotti describes a female patient of 31 who suddenly fell ill under the image of abdominal porphyria. He found strong atrophy of numerous muscle-groups which led to an entire paralysis.

Also here no symptoms which made a polyneuritis likely. The disease lasted 70 days, and ended with death. In spite of the large quantities of copro- und uroporphyrin which were daily secreted with the urine, no anemia appeared, on the contrary, in the last weeks of the disease even an increase of the quantity of hemoglobin, and the number of red bloodcells was to be observed. Vanotti does not mention — alas — if symptoms of a raised activity of the bone-marrow failed. The secreted uroporphyrin belonged according to him to the III-group. He, too, points out the large quantities of the brown pigment also found by us which was secreted with the urine. This brown pigment was to proceed according to our opinion from the globinpart of the muscle-pigment. In the urine likewise proper quantities of creatinin were found; these were maintained till death just as the porphyrin. At the obduction were found important muscular changes. In most muscle-groups

porphyrins could be shown but in a few muscular parts, become quite atrophic, they failed. All the myoglobin had already left these muscle-fibres.

2. Meyer-Betz has described a patient with whom similar symptoms appeared, but with whom beside muscular paralyses a strong hemoglobinuria was observed. The aspect of the disease showed according to him great similarity with the *dystrophia musculorum progressiva*. He points out the distinct connection between this myoglobinuria and the injury to the muscles.

3. Also Paul and Gunther described a similar aspect with hemoglobinuria at which the muscles showed a waxy degeneration. Moreover we found in literature two similar cases of Kratzenstein and of Pol. In both cases it was paroxysmal attack at which in one case myoglobin, and in the other myoporphyrin was secreted. Also in Norwegian literature a case is known in which every time after catching cold a porphyrinuria was developed, attended with fever, violent stomach-aches and ileus-symptoms. In these cases it has however not been demonstrated spectroscopically that one had to do with myoglobin; no more have creatinin-estimations been performed, and for the rest these cases have not been sufficiently reproduced clinically either, to give sufficient support to the supposition that one has to do here with the muscle-pigment. Yet we believe that there are sufficient arguments to consider, in their cases, also the muscles as the place of formation of these globin-pigments.

When we regard now once more some processes of diseases of porphyrin-patients, formerly observed by us, facing the possibility of a myoporphyrin and at the same time trace accurately the many cases described in literature (especially the one hundred patients described by Waldenstrom in the *Acta Medica Scandinavica*), then the following strikes us:

1. With several of these patients we see that during the attack with a mortal or not mortal turn no anemia appeared. Waldenstrom mentions this fact.

2. In many cases, also in very severe ones, any disturbance of the sensibility fails, and in most cases the reflexes were still present a long time or less distinctly, also then, when the patients were no longer able to use these muscles. Also the order of succession in which the paralyses appear, is usually very arbitrary.

Most writers mention that the disease progressed under the aspect of the Landry-paralysis, but when the development of the pareses and paralyzes is considered, a really typical increasing paralysis is yet most rarely found.

One gets the impression that among these cases there are a rather large number in which a more accurate study should have led to the diagnosis of a myoporphyria. But of this possibility formerly was not thought virtually and so not further gone into at the examination either.

We have the impression that the aspect of myoporphyria is not so rare, and that it will be diagnosticated oftener, if only the necessary attention is paid to its possibility of existence. Via myoporphyria and myoglobinuria then gradually a greater interest will develop itself for the destiny of myoglobin, on which physiology, and especially the clinic have so far not lavished their gifts.

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## Diabetic Coma.

A 9 year statistical record,

By

JOHS. HAGTVET.

(Submitted for publication January 18, 1943).

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»Diabetic coma remains the  
peculiar problem of diabetics».

I.

J. P. Joslin (1937).

From certain quarters it has been maintained that in recent years the frequency of coma has been rapidly declining. This tendency is said to have become especially noticeable since the introduction of the slowly absorbable insulin preparation Retard and after the adoption of a freer use of carbohydrates in the diet.

From other quarters, on the contrary, it is pointed out that coma is still a common occurrence and that deaths in coma continue to form a large proportion of the mortality from diabetes.

In 1934 O. Stub published a statistical record of the cases of coma treated in the University Clinic med. Dept. A., in the years from 1924 to 1932. Nine years have now elapsed since that publication appeared, and during this period the situation has undergone changes in many respects. Our knowledge regarding insulin has become more complete. In 1934 came the slow-acting insulin, Retard, and later the Zinc-protamin insulin. Dietary treatment has become a matter of secondary importance since the freer use of carbo-

hydrates has been introduced. The diabetic's lot is being rapidly improved: His life-time is prolonged and his mode of living is constantly coming nearer to that of the healthy individual, thanks to a more rational system of control for diabetics. In the altered situation new problems are constantly arising. The diabetics now often reach the time of life when they are subject to the complications due to advanced age, and diabetic women become pregnant.

The study of the electrolytic changes during acidosis has led to the adoption of new views regarding the treatment of diabetic coma. Alkali treatment has again come into favour and is the subject of lively discussion.

When now taking up for renewed investigation the material at disposal from the University Clinic<sup>1</sup>, we have chosen a period of nine years in order to get criteria for a comparison with O. Stub's statistics. By employing the same mode of procedure as O. Stub, we believe that an individually serviceable basis of comparison can be obtained.

The great majority of the diabetic patients come from the rural districts, from the broad valleys of East Norway. The hospital keeps in contact with the patients by facilitating their admission for control of condition and for treatment of complications.

In its general principles the mode of treatment practised in the Clinic does not differ particularly, except in dietetic details, from that commonly employed at present. It seems that the principle of the golden mean has been adopted, the regimen being made so simple as possible. The patient's manner of life is brought as close as possible to the normal, but he must respect his illness. The diet is not «free», but is of varied composition with restrictions as regards carbohydrates. The use of large quantities of vegetables has been abandoned, but most of the patients, who, as already mentioned, come from the country districts, are recommended a moderate daily amount. The supply of calories shall be limited, but sufficient to ensure fully capacity for work and an average body weight. Zinc insulin has been little used. Importance was attached to a systematic instruction of the patients in the elements of dietetics and the main points in the pathology of the disease. This is

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<sup>1</sup> The investigation was carried out with support from the Ivar Bang Memorial Fund.

Table 1. *Number of diabetics treated.*

	<i>New admissions:</i>			Total admissions.
	M.	F.	Total	
1/6--31/12—1932:	10	20	30	55
1933:	40	39	79	174
1934:	47	41	88	130
1935:	49	58	107	168
1936:	37	52	89	171
1937:	51	57	108	186
1938:	48	44	92	184
1939:	50	45	95	185
1940:	40	31	71	155
Till 1/6— 1941:	10	8	18	50
	382	395	777	1408

attained by going through with the patient a book published by Professor O. Hanssen for that purpose (2).

The low carbohydrate diet formerly used, is still employed to a certain extent. When acidosis is not imminent, an attempt at »desucration» is made at first. In this way the end in view, namely, an adequate adjustment, is not infrequently attained more rapidly than by at once proceeding to give full diet with insulin.

In the 9-year period, from June 1st 1932 to June 1st 1942, altogether 777 new cases of diabetes were treated in Medical Dept. A, while the total number of admissions for the disease (1408) was about double that figure. Ages: youngest 10 years, oldest 83 years. The patients are almost equally distributed between the two sexes (Table I). While the total number of admissions increases from year to year, the number of new cases remains fairly equal in the two periods of investigation.

Sixty-two patients were admitted in a state of coma or precoma. In distinguishing between these two conditions we lay chief weight upon the purely clinical judgement of the state, regarding the varying degrees of unconsciousness as the resultant of a series of pathological metabolic factors, each of which in itself is insufficient to account for the acidotic condition. In coma the patient is completely unconscious and elaborate measures are demanded

Table 2. Number of cases of coma and precoma treated.

	M.	F.	Total	Whereof died:		
				M.	F.	Total
From 1/6—1932:	4	2	6	1	0	1
1933:	4	5	9	0	1	1
1934:	2	1	3	0	0	0
1935:	5	4	9	1	0	1
1936:	3	7	10	1	1	2
1937:	0	8	8	0	1	1
1938:	6	2	8	1	0	1
1939:	0	0	0	0	0	0
1940:	6	3	9	1	1	2
Till 3/6— 1941:	0	0	0	0	0	0
	30	32	62	5	4	9

in order to get rid of the acidosis. We call it precoma when the patient is stuporous, but reacts to physiological stimuli and can swallow liquids. This state may arise whether the alkaline reserve is under or over 20 vol. per cent.

Of the 62 coma patients 9 died, 5 men and 4 women.

The coma cases are distributed (Table II) comparatively evenly throughout the period of investigation, with the exception that no case of severe acidosis was treated in 1939. The frequency of coma, in proportion to the total number of diabetics treated, is found to be 4.4 per cent (O. Stub 9.4 per cent). Of the 62 patients 52 were admitted once, 2 patients twice, and 2 patients three times.

Table III shows the degree of consciousness on admission. Of the 62 patients 11 were comatose, with 7 deaths, while of the 51 soporous or stuporous patients 2 died, thus illustrating the well-

Table 3. Degree of consciousness on admission.

	Number:	Whereof died:
Coma	11	7
Precoma: Stuporous	18	2
Soporous	33	0
	62	9

Table 4. *Duration of diabetes when coma set in.*

	M.	F.	Total.	Where of died:		
				M.	F.	Total.
0—½ year:	7	6	13	1	1	2
½—2 years:	4	5	9	0	1	1
2—4 years:	7	10	17	1	0	1
4—6 years:	2	4	6	1	1	2
6—8 years:	5	3	8	1	1	2
8—10 years:	2	2	4	0	0	0
Over 10 years:	3	2	5	1	0	1
	30	32	62	5	4	9

known fact that the entirely unconscious diabetic has a greatly reduced chance of living as compared with the stuporous patient. It can at once be remarked that for a large proportion of the stuporous patients the alkaline reserve was so low that at the least they come within Joslin's definition of coma.

The duration of the diabetes at the time when coma set in is seen from Table IV. 13 of the patients had presented symptoms during half a year before coma supervened. In this group there were two deaths.

The age distribution among the coma patients is shown in Table V. There is a clear preponderance in the younger age-classes, half of the patients being under 30 years old and the majority of these in their second decade of life. All those between 10 and 20 years old recovered. Otherwise the deaths are evenly

Table 5. *Ages of patients with coma.*

	M.	F.	Total.	Whereof died:		
				M.	F.	Total.
10—20 years:	13	7	20	0	0	0
20—30 years:	5	8	13	1	1	2
30—40 years:	4	4	8	1	0	1
40—50 years:	3	6	9	1	1	2
50—60 years:	4	2	6	1	1	2
60—70 years:	1	4	5	1	1	2
Over 70 years:	0	1	1	0	0	0
	30	32	62	5	4	9

distributed, without the marked excess mortality among older patients which is revealed in other statistics, including O. Stub's. Baker believes that the oldest patient reported in the world literature to have recovered was 74 years old. It is seen that among the cases of recovery in our hospital there was a still older patient, a woman aged 83 (who had had 16 children).

When we reckon out the percentage of mortality from the small figures available it is found to lie at 14.5 per cent, as compared with 30.5 per cent in Stub's material. This might perhaps be taken as indicating an improvement in the patients' chances of recovery, although many irrelevant factors may come into play in the two groups of material. It is natural to ascribe the improvement to better control of diabetics. We no longer meet with so many neglected cases. In a statistical record from the Mayo Clinic, comprising 108 cases of diabetic coma Th. Baker (3) reports a total mortality of 15.7 per cent.

The blood sugar values on admission were as follows:

Table 6.

Under 500 mg %	500—600	600—700	700—800	800—1000	Over 1000
33	10	8	7	2	2
Whereof died: 0	1	4	2	2	0

No correlation could be noted between the blood sugar and the degree of coma.

The average consumption of insulin was 232 int. units in the first 24 hours, and 104 in the second, with an upper limit of 600 units. For comparison may be mentioned Joslin's (9) average amount of 252 units (in the period 1929—1931).

Of greater interest is an examination of the incidental causes which brought on the state of coma (Table VII). In most cases the cause is of complex nature, but always seems to consist in the use of too little insulin in proportion to carbohydrates. Irregularities of diet and of insulin led to coma in 34 cases. In 13 of these cases *dietary irregularities alone* constituted the main cause. Two patients were by other doctors put on «free diet», which resulted in coma. The unfortunate effect of this regimen, or absence thereof,

Table 7.

Group 1:	Irregularities of diet and insulin: .....	21	} 34
	No treatment before coma set in: .....	11	
	Low carbohydrate diet: .....	2	
Group 2:	Infections:		
	Diseases of respir. tract (colds, rhinitis, angina):	9	} 24
	Pneumonia: .....	3	
	Dyspepsia, gastroenteritis: .....	3	
	Gumboil, toothache: .....	2	
	Pyuria: .....	2	
	Catarrhal jaundice: .....	1	
	Abscess + sepsis: .....	3	
	Phlegmone: .....	1	
Group 3:	Other causes:		
	Pregnancy: .....	2	} 3
	Apoplexy, nephritis: .....	1	
Group 4:	Unknown cause (progression of illness?): ....		1

from a didactic standpoint is that the patient is inclined to loose the respect for his disease, which cannot be done with impunity.

*Omission of insulin* was the principal cause in six cases. Three of these patients suddenly ceased to use the remedy on the advice of a well-known quack (homeopath). One of them, a woman, actually adopted a diet of pork and cabbage and as early as 24 hours afterwards showed symptoms of severe acidosis. In spite of energetic treatment she could not be roused from the state of coma. Two others escaped with their lives in spite of severe intoxication. The rapid setting in of grave acidosis observed on cessation of insulin treatment was remarkable. It seems obvious that the system had adapted itself to the remedy and had allowed its defensive mechanism against acidosis to come out of action. A woman who, apparently with suicidal intent, three times discontinued the use of insulin fell each time into coma or precoma.

In the same connection must be mentioned the formerly usual low carbohydrate diet. As early as in 1899 Jens Bugge, who was then Clinical assistant of this department, warned against an incautious employment of this diet. In the more serious cases of diabetes it may lead to coma. In the present material two such cases occur, so that the warning must still be said to have actuality.

For as many as 15 of the patients admitted in a state of coma this was the first manifestation of diabetes diagnosed. One of them died in that state, that is to say, before the insulin treatment had got a fair chance. In Stub's material there were 7 such cases. This is a point of great importance as regards our prophylactic measures against coma.

The well known effect of infection in bringing on coma was revealed in 24 cases. This is a quite regularly recurring observation and is of importance for the prophylaxis: The patient gets an inter-current infection which brings about anorexia or vomiting. The patient (or in a few cases the doctor) then concludes that the dose of insulin must be diminished, corresponding to the reduction in the quantity of carbohydrates consumed. The fear of hypoglycemia is greater than the fear of acidosis, and the use of insulin is then discontinued in a situation where it is most needed. The result of this will very soon be seen.

Of the 24 infections the majority were slight everyday maladies, such as «colds» and «influenza». No infection is without significance for a diabetic, but the most dangerous are those which cause vomiting and diarrhoea. Under unfavourable circumstances even a toothache may start the wheel of fate, as was the case with a 24-year-old diabetic woman. She got a headache one day and the doctor gave her an antipyretic remedy. The next day she was drowsy and at midday she was found lying in bed in a comatose state. When admitted to the hospital the same afternoon she was moribund.

Of the 9 patients who died, 6 had an infection (sepsis + abscess of prostate and lungs in two cases; advanced phlegmone and abscess in another two cases; acute hepatitis and symptoms suggesting pneumonia in one case each). All six died in a sepsis-like condition, some of them far out in the course of the illness, at a time when the diabetes was well under control, and without acidosis. In these cases the infection seems to have assumed an unusually torpid character, with little power of reaction in the organism. The majority of the coma patients with infection were free from fever when admitted to the hospital, so long as the acidosis was severe. One must search high and low for a focus of infection in spite of the temperature being normal. The counting of leucocytes fails to give any guidance in this respect, seeing that up to



50.000 white blood corpuscles per  $\text{mm}^3$  may be found in non-complicated cases of coma.

Two of the comatose patients were pregnant. The tendency to acidosis in such women is a well-known experience, and calls for great vigilance, even when there are no complications. With the doses which keep the blood sugar well controlled, distinct symptoms of ketonuria may often be observed.

One patient showed hypophyseal changes (small sella turcica), and pronounced hirsutism (beard and abnormal hairiness of the body).

The observations and practical conclusions which we derive from statistics and which at any rate hold good for our clientele, are the following:

The frequency of coma is still great, even though it is decreasing. The percentage of deaths has been reduced, probably because the patient come under treatment at an early stage. Among the causative factors, infection play an important part, especially for the malignant forms of coma which results in death. While much improvement has already been attained in the care of diabetics, we can still have hopes of saving several lives by further development of the systematic supervision of such patients. Both patients and doctors must be prepared to pay closer attention to the insidious approach of coma under the mask of commonplace maladies. It is a mistake to refrain from giving insulin to a patient with acidosis until he has been conveyed to the hospital. On account of the long distances in Norway the general practitioner may be obliged to undertake the first treatment of the patient himself. If small doses of insulin (5—10 Leo units) are given every hour or half-hour, with frequent examination of urine, the danger of hypoglycemic shock will be small, and can be still further reduced by injections of glucose.

## II.

As a result of investigations made in the last few decades, especially by Van Slyke's school, the term acidosis is now being given an extended signification. Acidosis is defined as a disturbance of the organism's electrolytic balance of its acid-base equilibrium. Acidosis is an attack directed against the regulation-mechanism for the maintainance both of the hydrogen-ion concentration and

the osmotic pressure, as well as the mutual distribution of the electrolytes of the body fluids. Practically speaking, all electrolytes are influenced, but the disturbance affects especially the distribution of the anions. With any marked degree of acidosis the fixed alkalis are reduced and the coma is the result of a loss of bases which causes profound disturbances in the activity of the cells, not least in the kidneys, with the secondary consequences resulting therefrom. The coma must be treated from biochemical standpoints.

In this material, the alkaline reserve in 52 of the coma patients was determined at the time of admission. The average at that time was 20.5 vol. per cent. Deducting the patients to whom insulin was given some hours before admission, the  $\text{CO}_2$  combining-power was 18 vol. per cent. (Baker's statistics: average alkaline reserve on admission 15 vol. per cent.) Joslin fixes the limit for coma-precoma at 20 vol. per cent.

No constant relation between alkaline reserve and degrees of unconsciousness is found to exist in our material. At any rate 20 vol. per cent was not a certain limit. The lowest value, 9 vol. per cent., was noted in the case of a hospital nurse who was just barely soporous. Comatose patients might be found to have values over 25 vol. per cent., and another nurse, who was twice admitted to the hospital in state of precoma, was equally soporous with 13 as with 25 vol. per cent. The younger patients can evidently tolerate a low alkaline reserve better than the older; patients with infections become rapidly soporous.

The relation between alkaline reserve and mortality is illustrated by Diagram 1. The cases in our material are too few to admit of drawing any definite conclusions, but no fixed correlation can be said to exist. The same also appears from Baker's statistics.

During treatment with insulin and salt solution the  $\text{CO}_2$  combining-power increases steadily and with comparative rapidity, at any rate to a certain level. Nevertheless it is a clinical experience, which we have often noted in this material, that complete restitution sometimes fails to take place in spite of energetic treatment. Clinically we then find that a certain degree of hyperpnea persists, and the improvement in the general condition of the patient does not keep pace with the chemical improvement in blood sugar and

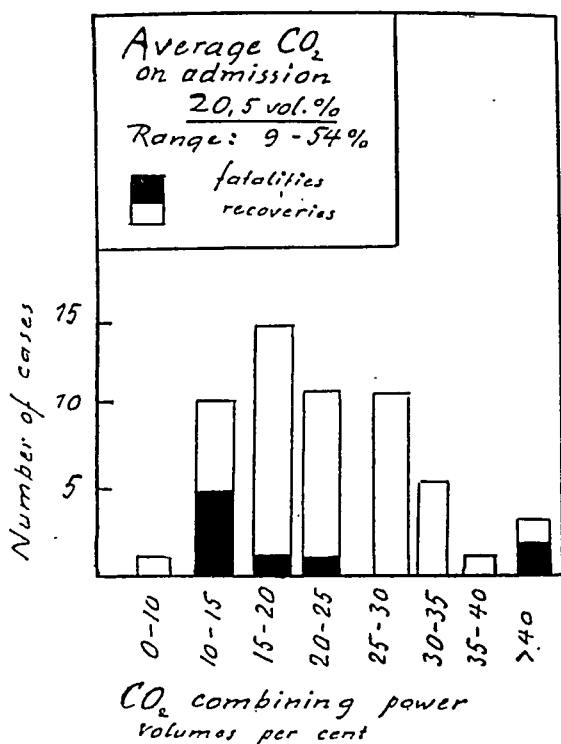


Diagram 1.

ketonuria. The sensorium does not clear up satisfactorily. The therapeutic measures demanded as a logical consequence of these observations (peroral or parenteral administration of bicarbonate) were adopted long before the study of electrolytes became general. As early as in 1910 Professor Olav Hanssen in this hospital was the first in Scandinavia who restored a comatose diabetic to consciousness by treatment with alkalis (3). In a monograph published in 1911 (4) he sums up as follows: »In case of acute diabetic intoxication administration of alkalis may bring the patient over the critical stage.»

The indications for use of the treatment in our department have been: 1) Extremely low alkaline reserve values, mostly under 15 vol. per cent. 2) The fact that the alkaline reserve fails to show signs of full restoration after glycosuria and ketonuria have disappeared. Special attention is paid to the behaviour of the sensorium and the respiration. The bicarbonate was administered in isotonic solution (1.3 per cent) or in 5 per cent solution, sterilized in seltzer bottles. When the patient is conscious, we preferably

give the bicarbonate per os. In recent years we have employed Palmer and Van Slyke's monogram for the dosage.

In 9 of the 62 cases bicarbonate treatment has been carried out methodically. In most cases it is recorded in the case report that the general condition improved and the respiration became natural directly after use of the remedy, the alkaline reserve becoming normal.

The reaction of the urea during acidosis was carefully followed in case of 24 patients by means of tests made at regular intervals. On the day of admission the content of urea in these patients varied as follows:

Table 8.

Under 50 mg p. c.		50—100 mg p. c.	100—150 mg p. c.	150—200 mg p. c.
Patients:	8	6	7	5
Deaths:	0	1	3	2

In many cases the alkaline reserve and the blood urea varied in inverse order, but this was not always the rule. The chlorides also probably take part in this interaction, but there were made no sufficiently systematic tests to permit of a closer discussion of the correlation. The importance of urea retention undoubtedly differs according to whether the total base values are reduced or not, whether the retention occurs during dehydration or later. Azotemia persisting or actually increasing in the post-comatose stage has for us always been an ominous prognostic sign.

Of late years we have devoted more attention to the behaviour of the chlorides, especially in the cardiovascular forms of coma. Peters and his collaborators (7) in America (1925) and Professor H. Salvesen's (6) publications in America and here in Norway have shown the significance of the chlorides as an important regulator of neutrality. They also lay most stress upon the loss of bases, with consequent profound disturbances of the electrolytic balance. A rather severe acidosis may arise without the concentration of bicarbonate being materially affected. In these cases the content of chlorides in the blood is small and the sodium for neutralisation of the ketonic acids is taken from the chlorides, whereby a saving of bicarbonate is effected. The action on the electrolytes of the

A.B. p. 73 years...

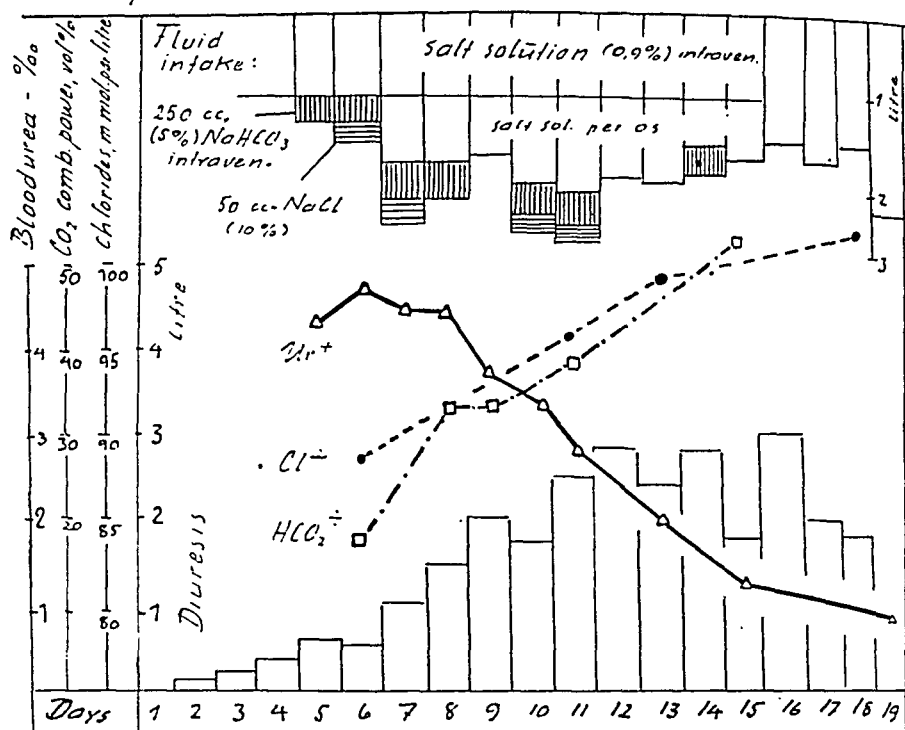


Diagram. 2.

blood depends on the severity and duration of the ketonemia, so that a slow development during a rather long period usually affects especially the chlorides. Salvesen draws attention to the low total-base values and the hyponatremia in grave forms of acidosis. Saline infusions have not only the effect of stopping the process of dehydration, but also a direct neutralizing action owing to the quantity of sodium given off by the salt.

The chlorides will be the direct point of attack for therapeutic measures when the reduction is so great that it is not checked by the chloride present in the quantities of saline solution usually administered. In cases with anuria and threatening circulatory collapse high degrees of hypochloremia have been observed. Rooth (5) has reported from Joslin's clinic several cases of coma with severe azotemia after intravenous injection of 60—130 cm<sup>3</sup> of 10 % NaCl. This course is recommended in cases where the anuria is not remedied by administration of large quantities of saline solution.

In our material we have an example of complicated electrolytic disturbance, where the action of salt solution and bicarbonate had a convincing effect.

A. B. — Woman aged 73.

In 1921 diabetes mellitus was diagnosed. In 1937 she began to use insulin. 8 U. of regular Insulin in the morning. On admission to the hospital the same year she was found to have hypertonia. 200/100 mm Hg and slight albuminuria. She was treated with 32 U. Retard and a mixed diet with about 90 g carbohydrate. During this treatment she excreted small quantities of sugar. No ketonuria. Before admission for the second time, in 1941, she had for about six months presented symptoms of gall-stone. After being free from symptoms for two weeks she got a typical attack of cholecystitis, with shiverings, temperature approaching 39° C, increasing serum-colour, as well as pains and tenderness under the right costal arch, where an enlarged gall-bladder could be palpated. No vomiting. After five days the attack subsided. During the whole time the supply of salt solution was kept at over 2000 cm<sup>3</sup>. The diuresis varied between 1000 and 100 cm<sup>3</sup>. The blood sugar content was kept well regulated, and there was no ketonuria.

In spite of freedom from fever and pains and the abatement in symptoms from the bile ducts, the patient sank into a drowsy state, became soporous, unclear and sometimes disturbed in mind. The albumen reaction in the urine became and remained more strongly positive. The blood pressure fell to 145/80 mm. No change in respiration. She began to itch very much, and her breath smelt of urine. The diuresis diminished and attacks of vomiting set in. A blood-urea test now showed 423 mg per cent, the alkaline reserve was 17.6 vol. per cent and the chlorides in serum 85.8 milli-equivalents per litre. A copious parenteral administration of salt solution was now commenced, with addition of almost every day of 50 cm<sup>3</sup> of 10 % NaCl and 250 cm<sup>3</sup> of 5 % NaHCO<sub>3</sub> intravenously. The reaction of the diuresis and of certain constituents of the blood is shown in the diagram (No. 2).

The clinical effects of administration were highly convincing: During, or immediately after injection of the solution of salt and bicarbonate the patient woke up, became clearer in mind and began to take drink of her own accord. The diuresis did not increase materially until the 5th day after commencement of this treatment.

After the lapse of 14 days the clinical remission was complete, and at the same time the blood values became normal. During the whole course of the treatment the blood sugar was well regulated and there was no ketonemia. In the later courses the renal functions were found to be normal.

Of cardiovascular forms of coma we have in these nine years treated three cases in which symptoms from the circulation or from the kidneys dominated. In others the cardiovascular element

manifested itself by falling blood pressure, weak pulse, oliguria and bad general state of health. Energetic treatment with insulin and salt solution eventually remedied the condition. One patient's case was almost hopeless, when we gave him a transfusion of blood with striking effects.

In one case the renal function was tested during the coma by urea-clearance. It had been reduced to about 20 per cent of the normal. After recovery from coma the functioning was found to be normal.

Diabetic acidosis still presents a number of unsolved problems. There is reason to believe that further study of the electrolytic displacements in coma may furnish data for an improved method of treatment.

### Summary.

1. The author has made a statistical examination of the cases of diabetic coma treated in the medical department A of the University Clinic, Oslo, Norway, in the period from 1932 to 1941. Altogether 777 diabetics were treated, the total number of separate admissions for the disease being 1408. Sixty-two of them were admitted in a state of severe acidosis, the youngest being 9 and the oldest 83 years old. Compared with the records of the preceding 9-year period from the same department the frequency of coma shows a decrease, from 9.4 to 4.4 per cent., and the mortality from coma has fallen from 30.5 to 14.5 per cent.

2. The average alkaline reserve on admission was 20.5 vol. per cent (Adjusted: 18 per cent). No fixed correlation is found to exist between alkaline reserve and mortality, nor between the degree of unconsciousness and the alkaline reserve. In advances age and in case of infection coma may rapidly supervene.

Bicarbonate treatment was employed in about 15 per cent of the cases. The indication for such treatment were 1) low alkaline reserve (mostly under 15 vol. per cent) and 2) incomplete restoration in the post-comatose stage.

3. The practical experiences and conclusions drawn from perusal of the case-records go to indicate that much can still be gained by prophylactic measures. Information both from patient and doctor as to measures adopted in case of complications, and espe-

cially of infection, is still needed. For a large proportion of the patients (15 out of 62) coma was the first manifestation of diabetes diagnosed.

4. In a case of cardiovascular coma a dramatic improvement was obtained by transfusion of blood. The electrolyte disturbances in diabetic acidosis is mentioned. A case with complicated electrolytic disturbance is described. The modern methods of acidosis treatment comprise regular examinations of alkaline reserve, urea, blood sugar, chlorides and total-base metabolism.

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(Chief Pathologist: Svend Petri, M. D.)

## On the Changes Produced by Experimental Resection of the Fundus of the Stomach in Pigs.<sup>1</sup>

By

SVEND PETRI, FLEMMING NØRGAARD, KJELD TRAUTNER  
and WILLIAM KIÆR.

(Submitted for publication January 18, 1943).

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### Introduction.

In pups, total gastrectomy (including resection of the Brunner-gland area of the duodenum) produces constantly a severe, most often chronic, fatal neurocutaneous symptom complex — »experimental endogenous (gastroprival) pellagra» (Petri and collaborators, 1936). The lesion which subsequently has proved constantly reproducible in pigs too (after total gastrectomy alone) is clinically and morphologically identical with pellagra in man and with feeding pellagra in swine and dog.

Through a number of years efforts have been made to elucidate the causation of the experimental endogenous pellagra through three concurrent groups of experiments, some of which have been concluded and published, while others are still going on.

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<sup>1</sup> Read before the Danish Pathological Association on October 14th, 1942. The studies reported here were carried out with grants of aid, first from the Michaelsen Fond, later from P. Carl Petersen's Fond; for a couple of years they were continued by private means and now they have been concluded with aid from King Christian X's Fond.

Translated from the *ap.* by Hans Andersen, M. D.

These experimental groups include investigations on:

1) the results of the same operation performed on animals of different species (total gastrectomy on pups, pigs, kittens and young rats);

2) the results of various, single or combined, elective resections of the stomach and small intestine in animals of the same species (pups, pigs); and

3) the amenability of the gastroprival pellagra to treatment with various therapeutics, primarily the injectible vitamins B (pups, pigs).

The studies reported in the following were commenced 6 years ago by one of us (Petri), aiming by subtotal or total elective resection of the fundus (on pigs) to elucidate the etiological significance of the fundus region to the appearance of gastroprival pellagra. The central nervous system from the older part of the material has been dealt with by Nørgaard in his dissertation on «Histological Changes in the Central Nervous System in Experimental Endogenous Gastroprival Pellagra in Swine and Dog» (Munksgaard, October 1942). Further, the liver material from some of the experimental animals has been used in our studies on the significance of the fundus region to the formation of the antipernicious-anemic principle of the liver (Petri and collaborators, 1941).

#### Previous Investigations.

Previously experimental resection of the fundus has been performed only on dogs.

Petri and collaborators (1935, 1936) observed in a very young, full-grown dog that this operation was followed in 4 months by the development of relatively mild normochromic and normocytic anemia which subsided somewhat in response to the following iron treatment (5 months) and subsequently increased again (3 months).

Vlados and collaborators (1936) produced in 16 dogs [with an observation period of 6 months (?)] a hyporegenerative anemia which appeared immediately after the resection and gave values as low as 40 % below the initial values, but spontaneous remissions appeared after 2—3 ½ months, and the bone marrow was normal; no other changes were noted.

### Writers' Investigations.

#### *Material, Technique, Observation Period, Diet.*

The *material* comprises 22 pigs, 8 of whom were submitted to subtotal resection of the fundus, 14 to total resection.<sup>1</sup> On some of these animals the development and course of the clinical and morphological changes were followed (7 animals with subtotal resection, and 7 with total resection of the fundus) — cf. A under »Observation Period». After a shorter or longer primary observation period the remaining animals were transferred to various therapeutic experiments (1 animal with subtotal resection, 7 with total resection) — cf. B under »Observation Period» — forming thus a clinical supplement to the first-mentioned group. The results of the therapeutic experiments will be reported in a subsequent paper.

#### *Operative Technique.*

As usual, the pigs were operated on at an age of about 8 weeks. In the first cases the fundus resection was performed on the basis of Meulengracht & Søeborg Ohlsen's schema of the extension of the fundus region in the stomach of the swine (1934).

Correspondingly, a fairly large, tongue-shaped middle area was excised from the anterior and posterior surfaces of the stomach, its base covering about two-fifths of the greater curvature, whereas

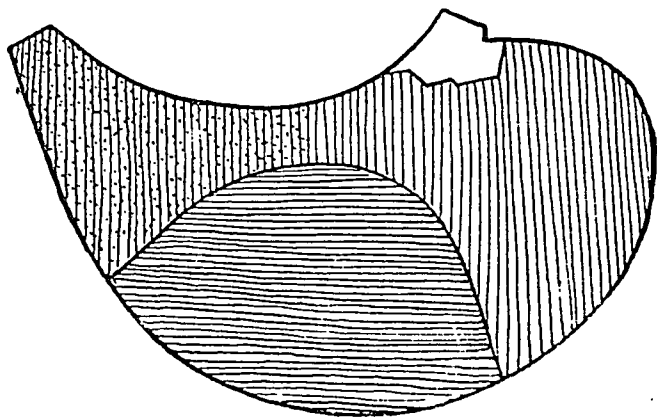


Fig. 1. Schematic presentation of the distribution of the cardia, fundus and pylorus glands in the stomach of swine (Meulengracht & Søeborg Ohlsen, 1934).

<sup>1</sup> An additional pig (No. 27) on which subtotal resection was performed, and which was observed only for 47 days (died with an abscess of the lungs) is not included in the account of the experimental material.

the area near the lesser curvature (in the cardia as well as in the pylorus) remained intact. Confident about the practical serviceability of this schematic topographical map of the stomach we did not consider it necessary to check up these findings by histological examination of the resection specimens. On autopsy, however, the animals were found to present a remnant of the fundus, showing that, contrary to our expectations, the resections had been merely subtotal.

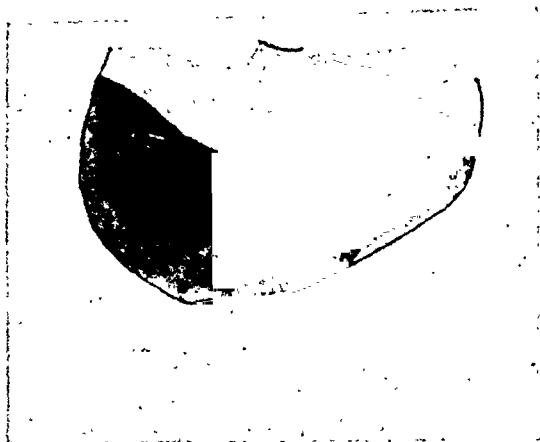


Fig. 2. Part of the stomach removed in total resection of the fundus (No. 124), showing the extension of the fundus region (black area). The lower border of the specimen is made up of the greater curvature; at the middle of the upper border, a part of the lesser curvature is seen.

In subsequent experiments, therefore, the extent of the resection was increased somewhat, being made as a regular transversal resection of the stomach. Of the greater curvature now a little more of the proximal part was removed; of the lesser curvature, only the distal two-thirds was left; the proximal incision for the resection passing just to the right of the oesophagus.

From the histotopographical examination of these later resection specimens it is evident that the fundus region, including its transitional zone (about  $\frac{1}{2}$  cm in width) has been removed completely together with the adjacent border of the cardia and pylorus (varying a little in width). The fundus region presents certain variations as to size, form and location, the details of which will not be entered into here. As to the technique of the operation, the greatest difficulty in the extirpation is presented by the process of the fundus region extending towards the oesophagus.

*Observation Period.*

A.	7 pigs with subtotal resection: min. 128 days; max. 499; aver. 314				
	7	•	•	total	• : • 67 • ; • 379; • 234
B.	1 • • subtotal • ;				
	7	•	•	total	• ; • 124 • ; • 252; • 195

*General Experimental Conditions.*

In this respect the present experiments correspond precisely to our previous experiments. For most of the animals the *diet* has consisted of crushed barley, crushed red maize, rye bread, milk, porridge, boiled potatoes and an addition of lime mixture and cod liver oil, now and then beets too. During the last year, when 5 of the pigs were submitted to total resection outer conditions have necessitated a modification of the diet, substituting the two first-mentioned components by larger amounts of bread and potatoes together with vegetables.

*Experimental Results.**Subtotal Resection of the Fundus.*

[8 pigs: No. 25 (observation period 499 days), 26 (128), 29 (345), 30 (461), 45 (224), 46 (217), 48 (324), and 47 (194); the last one (No. 47) was subsequently transferred to a therapeutical experiment.]

*Clinical Changes.*

In 4 of the animals only a transitory inhibition of growth was observed, together with minor changes in the blood picture.

In one of the 4 other animals (No. 26), these changes were associated with certain, rather severe, changes in the central nervous system, characterized especially by motor impairment. This condition may be designated as subacute pellagrous myelopathy.

In the remaining animals (Nos. 45, 46, 47) the usual inhibition of growth and minor changes in the blood picture, which appeared about 1 ½ months after the operation were accompanied by emaciation and changes in the skin and hair, whereas no clinical changes in the central nervous system could be demonstrated with certainty. The pellagrous symptoms remained stationary in No. 47 which subsequently was transferred to a therapeutic experiment; the two others showed respectively complete and almost complete

remission of the inhibition of growth and the skin and hair changes. This condition may be designated as stationary and partially remittent, chronic pellagra, respectively.

The appetite and defecation were normal in all the animals. Only one (No. 26) died spontaneously; all the others were killed.

From the weight curves (Fig. 3) it is evident that a moderate, exceptionally, a more pronounced, inhibition of growth has asserted itself for 5—10, less frequently 15, weeks after the operation — and this phenomenon was observed in every case. After this the growth has proceeded about normally throughout the observation period in the 7 animals, whereas the growth remained inhibited in one animal.

*Changes in the Blood Picture.* — At one point of time, all the animals were anemic, most of them persistently. In two of the cases the anemia was aggravated temporarily. At the time they were killed (or died) 7 showed a slight or moderate anemia, 1 a slight degree of isolated hyperchromic anemia. The anemia was slightly hypochromic (2) or slightly hyperchromic (5), with a tendency to macrocytosis (1) or normocytic (6). The isolated hyperchromia was slightly microcytic; at a previous juncture this animal had shown a moderate hypochromic anemia.

The white blood count was decreased (3), increased (4) or unchanged (1); the terminal values were: min. 8120, max. 20,760, average 15,355 (the initial values were min. 9640, max. 17,320, average 12,820).

### *Morphological Changes.*

*Macroscopic.* Apparently normal conditions were seen in all the 7 autopsied animals.

*Stomach:* The size of the resected stomach varied, being the least in the animal with the shortest observation period (No. 26), largest in 3 of the 4 animals with the longest observation period (Nos. 25, 30, 48), and of intermediate size in the remaining (Nos. 29, 45, 46). So, on the whole, the variations in the size of the stomach are proportional to the length of the animals. The greater curvature measured  $19\frac{3}{4}$  cm (No. 26), 31—35 cm (Nos. 29, 46, 45) and  $44\frac{1}{2}$ — $48\frac{1}{2}$  cm (Nos. 48, 30, 25). The form of the stomach corresponded fairly well to the normal. On the mucous surface the area covered by squamous epithelium at the inlet of the oesophagus was found to be increased in extension, and a larger zone of cardia and a smaller zone of pylorus were sharply defined as adjacent along the oblique resection scar. In immediate relation hereto, most often proximally, all the

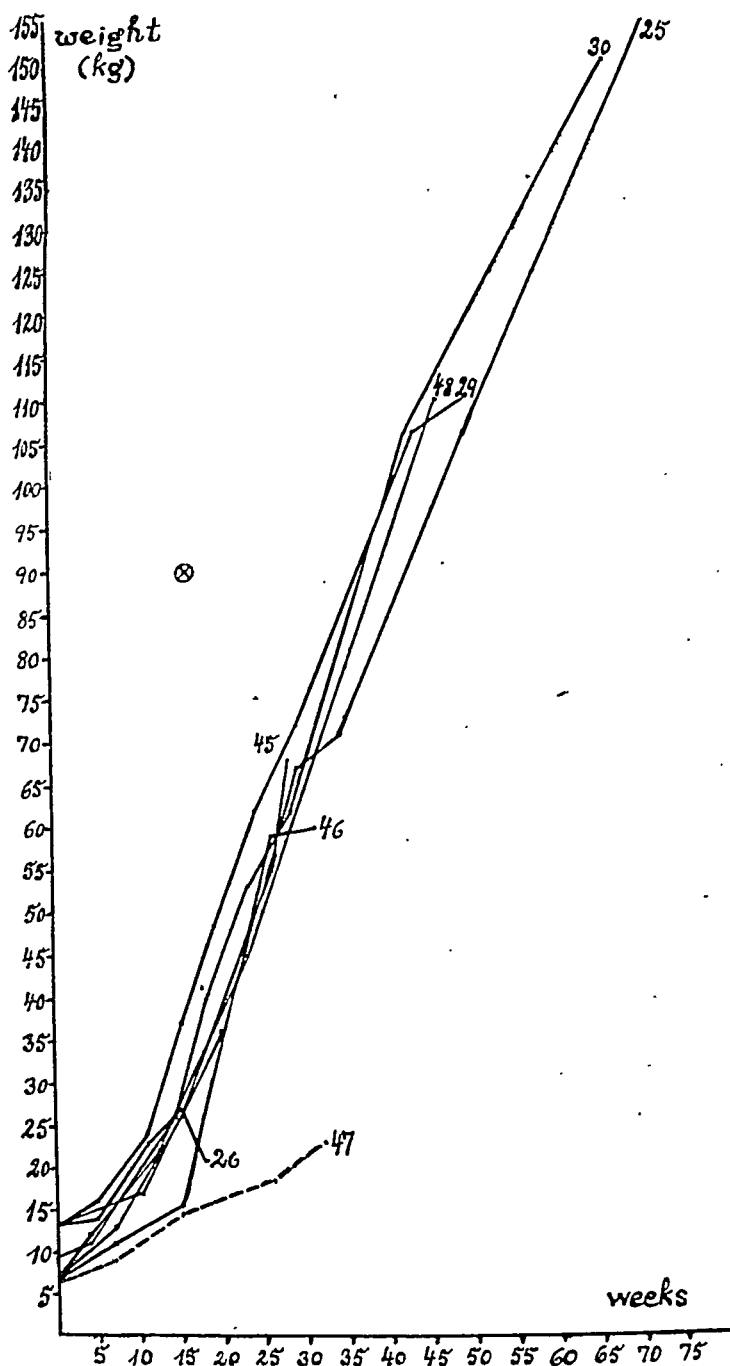


Fig. 3. Weight curves for 8 pigs on which subtotal fundus resection was performed at the age of 8 weeks.

The punctate curve (No. 47) corresponds to the 1' observation period for this pig which — in contrast to the others — was transferred to a therapeutic experiment.

The mark to the left, at the level of 90 kg., indicates the normal weight of a swine 6 months old.

animals presented an irregularly rounded or elongated, more prominent fundus region, coarsely folded or nodular. This remnant of the fundus which was noticeably larger than the area left at the operation — and considerably thicker than normally — was seen constantly, though varying somewhat in size, on both the anterior and posterior surfaces of the mucous membrane. This remnant of the fundus was smallest in the animal with the shortest observation period (No. 26) and relatively small also in one of the 4 animals with the longest observation period (No. 48); it had attained its largest size in the animal with the second longest lifetime (No. 30); and in the other cases it was about of the same size. Thus there is some disproportion between the size of the fundus remnant and the length (age) of the



Fig. 4. Stomach showing hypertrophy of the fundus remnant after subtotal resection of the fundus (No. 29). The more extensive area of squamous epithelium is seen above; in the middle, the oblique scar and, adjacent hereto, on both sides, the rather prominent, well-defined remnant of the fundus.

animal. The minimum measure of the fundus remnant was  $2\frac{1}{2} \times 2\frac{1}{4}$  cm on the anterior surface, and  $2 \times 1\frac{1}{2}$  cm on the posterior surface (No. 26); the maximum measure was  $11 \times 9$  cm and  $7 \times 6$  cm (No. 30).

To what extent the cardia and the pylorus region take part in the compensatory enlargement of the stomach found on autopsy cannot be decided with certainty. Still, the pylorus appears to be relatively larger than normally.

All the other organs showed no macroscopic abnormalities except for the presence of fibrillary adhesions in the peritoneal cavity.

#### *Microscopic.*

Stomach: The mucous membrane of the fundus remnant had undergone hypertrophy in varying degrees, measuring up to 4 times the normal in thickness. The glands were noticeably enlarged, containing secretion. The



subcutaneous oedema, and a certain degree of spontaneous remission. The appetite and defecation were normal; and a terminal diarrhea was seen only in the animals most affected.

In the remaining 2 animals, with a shorter observation period (Nos. 124 and 134), clinical pellagrous changes were very scanty or absent.

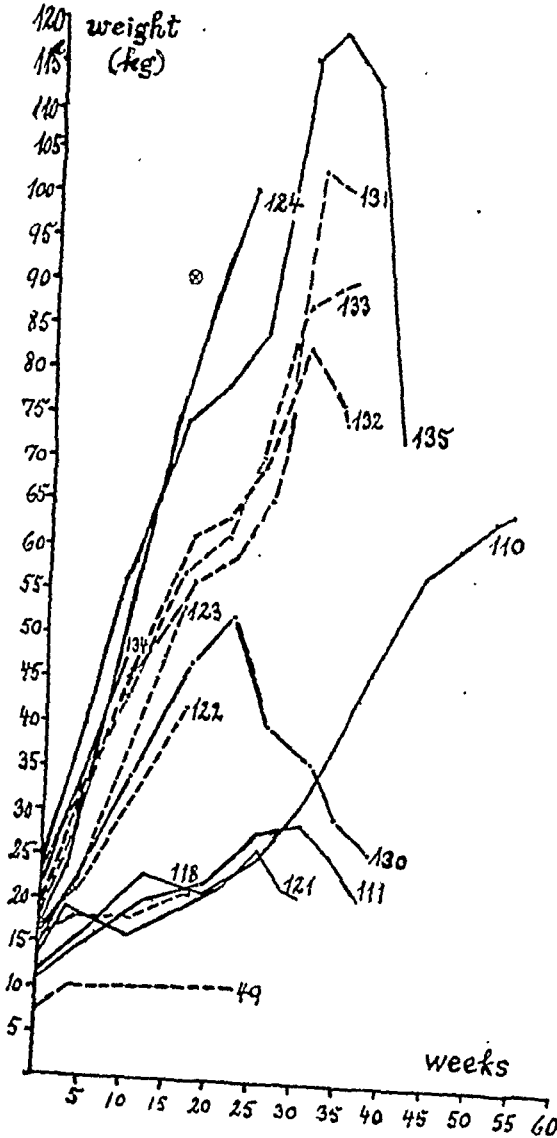


Fig. 5. Weight curves for the 14 pigs, on which a total resection of the fundus was performed at the age of 8 weeks. The punctate curves (Nos. 49, 118, 122, 123, 131, 132, 133) correspond to the 1' observation period for the pigs which — in contrast to the others were transferred later to therapeutic experiments. The mark to the left, at the level of 90 kg., indicates the normal weight of a swine 6 months old.

hypertrophy was least pronounced in No. 26, moderate in numbers 45, 46 and 48, pronounced in Nos. 25, 30 and 29. Like the duodenal mucosa, the gastric mucosa appeared otherwise normal, in particular, there was no increase in the lymphocyte content. The thickness of the mucous membrane appeared to be a little less than normal in the cardia, greater than normal in the pylorus.

The bone marrow showed normal conditions, corresponding to the age of the animals. Thus, after an observation period of 217 days (age of the animal about 275 days) the marrow as a rule was completely free from specific cells in the tibia and in the femur too. At about the same time, the proportion between marrow and fat cells in the vertebral bodies was 1:1; and this proportion kept fairly constant, even for the longest observation period, 499 days (age of the animal about 535 days).

Central nervous system: Thorough histological examination was carried out on 4 of the animals (Nos. 26, 29, 45, 46). In the remaining animals a control examination was made on the spinal cord. As to the nature of the changes, see below. The degree of these changes was marked in No. 26, rather slight in Nos. 45 and 46. The other animals in this group showed no changes in the central nervous system.

The other organs showed normal conditions except for certain slight and inconstant changes which appeared independently of the observation period and the size of the fundus remnant. These changes consisted in an increased content of eosinophil leucocytes in certain lymph glands (mesenteric) (Nos. 45 and 48) or small abscesses (No. 26); acute cholangitis (No. 26) or chronic periportal inflammatory infiltration (Nos. 26 and 48); commencing fibrinous ulceration of the mucous membrane of the small intestine (No. 26) or an increase in the number of eosinophil leucocytes in this structure (Nos. 29 and 46); hyperkeratosis and subacute dermatitis (Nos. 45 and, partially, 46).

### *Total Resection of the Fundus.*

[14 pigs: No. 110 (observation period 379 days), 111 (258), 121 (210), 124 (166), 130 (265), 134 (67) and 135 (290), besides the following pigs which subsequently were transferred to therapeutic experiments, No. 49 (180), 118 (124), 122 (161), 123 (157), 131 (252), 132 (248) and 133 (245).]

### *Clinical Changes.*

Of these 14 animals, 12 presented a clinical picture of pellagra, which, though varying in degree, was characterized by changes in growth, nutrition, skin and hair. In addition, they all showed some changes in the blood picture, especially as to the erythrocytic system. Further, after a fairly long observation period they constantly showed marked changes in the central nervous system. Of rare clinical changes, the following were observed: blindness,

subcutaneous oedema, and a certain degree of spontaneous remission. The appetite and defecation were normal; and a terminal diarrhea was seen only in the animals most affected.

In the remaining 2 animals, with a shorter observation period (Nos. 124 and 134), clinical pellagrous changes were very scanty or absent.

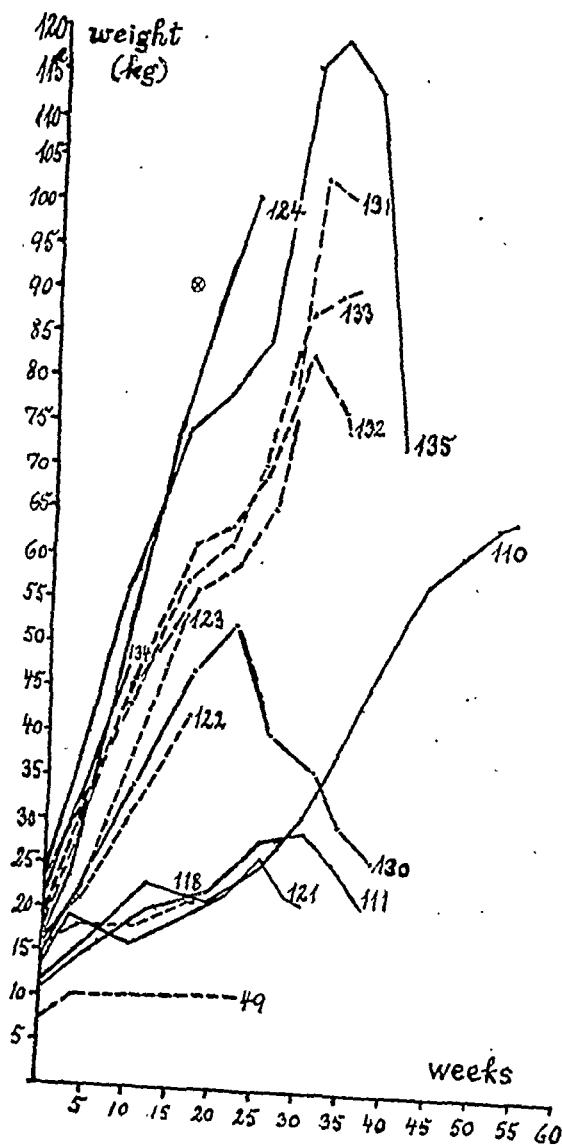


Fig. 5. Weight curves for the 14 pigs, on which a total resection of the fundus was performed at the age of 8 weeks. The punctate curves (Nos. 49, 118, 122, 123, 131, 132, 133) correspond to the 1' observation period for the pigs which — in contrast to the others were transferred later to therapeutic experiments. The mark to the left, at the level of 90 kg., indicates the normal weight of a swine 6 months old.

Of the 7 animals which were not transferred to therapeutic experiments, 2 died spontaneously (Nos. 111 and 130). The others, some of which were moribund, were killed by bleeding from a stab in the neck.

From the weight and length curves (Figs. 5 and 6) it will be noticed that 2 of the animals grew almost normally (Nos. 124 and 134). 5 animals showed a very marked inhibition of growth (arrest

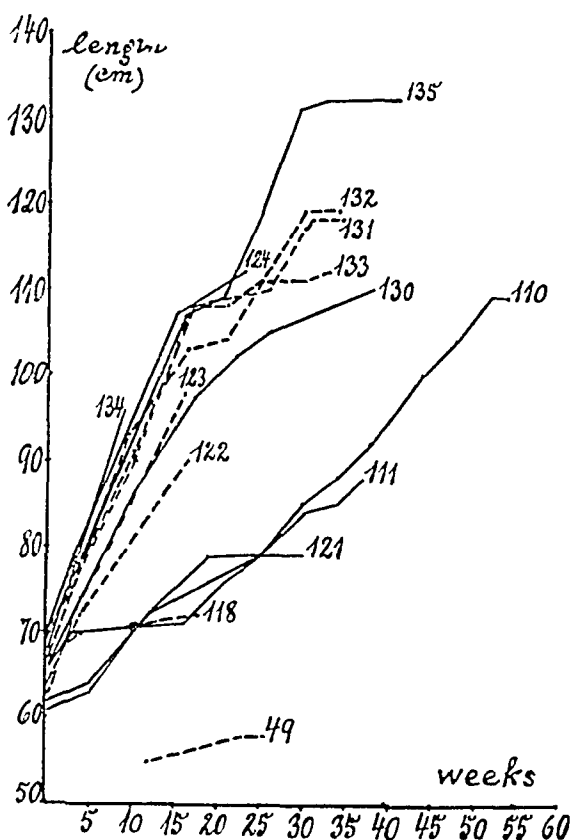


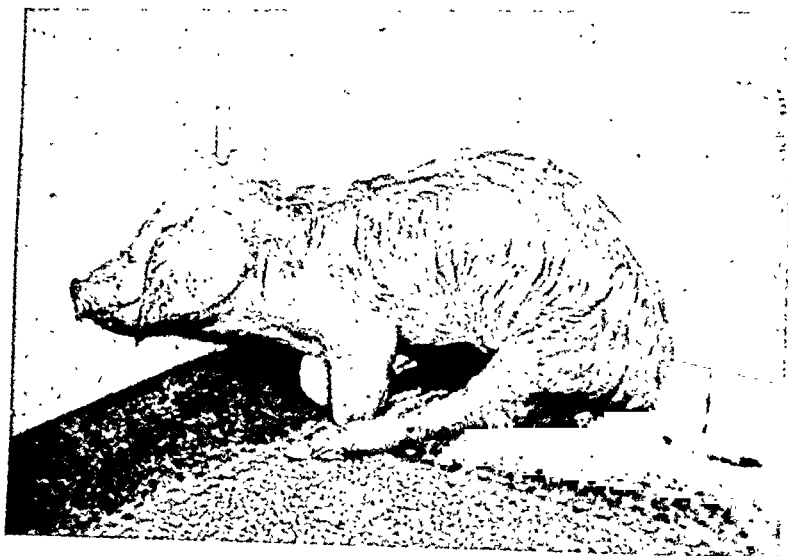
Fig. 6. Length curves for the same animals as in Fig. 5.

of growth») (Nos. 49, 111, 118, 121 and, to begin with, 110), while the remaining 7 animals showed merely a moderate and fairly equal inhibition of growth.

In 6 animals with a primary inhibition of growth (Nos. 111, 121, 130, 131, 132 and 135) the weight curve showed a rather abrupt fall in 22–33 weeks after the operation (cf. below: presence of circumscribed inflammatory processes); at the same time these animals ceased gaining in length, or their length increased but little. One of the animals with a marked primary inhibition of growth

(No. 110) commenced to grow spontaneously after an observation period of 6—8 months (cf. the tendency to spontaneous remission or some other symptoms too, but not for the changes in the central nervous system).

The nutrition was terminally either normal (less frequently) or moderate, marked or extreme emaciation.



Figs. 7—8. Total fundus-resected pig (No. 130) observed for 256 days, photographed 9 days before its spontaneous death. Weight: 28 kg. Length: 107 cm. Very marked clinical pellagrous changes: Arrest of growth, emaciation, skin and hair changes, anemia and, especially, marked changes in the central nervous system (the animal is about to fall from its erect (supported) posture, and it tries to get on its feet again).

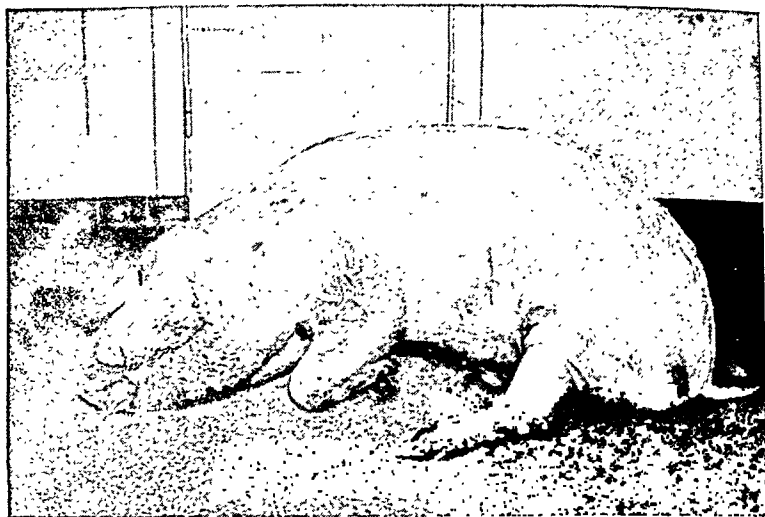


Fig. 9. Total fundus-resected pig (No. 135) observed for 248 days, photographed 42 days before it was killed. Weight: 112 kg. Length: 132 cm. This was the largest pellagrous animal in the groups and its nutrition was still good.

Principal clinical changes: Recent moderate changes in the central-nervous system (the animal resigns to a reclining posture after futile attempts to get on its feet).



Fig. 10. The two animals depicted above, here placed together for demonstration of the maximal difference in size of this group of animals. The foremost animal tries to move forwards.

they had some difficulty in getting on their feet. The back was kept curved, and the gait was slow, uncertain, with adducted hind legs. Gradually the difficulties in getting up and moving about increased, and finally the animal was almost completely incapable of these functions, so that as a rule it remained lying on its side with the forelegs strongly flexed, the hind legs extended, and the trunk trembling continuously. Often the emotional character was changed too, the animals becoming cross with a tendency to biting, but they did not become sluggish or drowsy. When they wanted to eat they moved forwards by crawling on flexed forelegs, with wriggling movements of the trunk and spastic movements of the hind legs. Attempts to get on their feet, by themselves or with support, were made by means of strenuous incoordinate kicking movements, during which the animal alternately dropped on its forelegs, or the hind legs slipped straight out anteriorly, to the sides or posteriorly; these failing efforts were accompanied by persistent and piercing shrieks (from pain or excitement?). When the animals were to be killed they exerted a quite considerable muscular power in their resistance.

In the remaining animals, with a relatively short observation period (up to 5—6 months) (Nos. 49, 118, 122, 123, 124, 134) no clinical signs of changes in the central nervous system were observed. (Still, No. 49 showed some emotional changes and terminally clonic convulsions; after the conclusion of the therapeutic experiments, the autopsy revealed the presence of an abscess of the brain.)

Junctures for the appearance of the clinical symptoms: In immediate sequence to the operation, changes were noticeable in the weight, nutrition and blood picture. Then, after a varying length of time changes were observed in the skin and hair too. The earliest manifestation of the changes in the central nervous system were respectively 155—191 days after the operation (Nos. 130, 121), but most often 245—253 days after (Nos. 135, 133, 132, 111, 131). In one of the first operated animals (the remittent case, No. 110), the presence of changes in the central nervous system was not noticed till rather late, when they had reached a severe degree (after 360 days).

The tendency to spontaneous remission (No. 110) manifested itself in an increase in weight, improved nutrition, marked diminu-

tion in the skin and hair changes and disappearance of the anemic features (with subsequent transition to polycythemia); on the other hand, the development of the changes in the central nervous system as to character and degree proceeded as in the other animals.

### *Morphological Changes.*

*Macroscopic.* In the 7 autopsied experimental animals the external appearance was normal in the 2 animals with a relatively short observation period (Nos. 124, 134). The remittent case (No. 110) showed only slight



Fig. 11. Stomach after total resection of the fundus (No. 124). The rather extensive area of squamous epithelium is seen in the upper part of the stomach. In the middle, the oblique scar from the resection can be made out between the cardia and the pylorus; no remnant of the fundus is seen.

skin changes. The remaining animals presented marked or very pronounced pellagrous changes (with regard to weight, nutrition, skin and hair); these changes were least pronounced, however, in the animal that primarily had shown the greatest increase in weight (No. 135).

*Stomach:* The size of the stomach varied somewhat, but on the whole it was fairly proportional to the length of the animal. The greater curvature measured from 19 cm (No. 121) to 30 cm (No. 124); in No. 110 it was not measured. The form of the stomach was fairly normal. On the mucous surface, the area lined with squamous epithelium, round the inlet of the oesophagus, was rather large; an increased cardia and a smaller zone of pylorus were sharply defined against each other, being adjacent along the slightly oblique resection scar. In no case could any remnant of the fundus be de-



monstrated in relation to this scar. As to the role played by the cardia and the pylorus region in the compensatory enlargement of the stomach revealed by the autopsy, no definite statement can be made; but the pylorus may possibly have been a little larger than normal.

Other organs: A relatively slight oedema and moderate ascites were observed in one animal (No. 121).

No less than 4 of the swine with a relatively long observation period presented circumscribed inflammatory processes in the form of fairly large abscesses of the lungs (Nos. 111, 121), a medium-sized subcutaneous abscess on the lateral surface of the thigh together with purulent pneumonia (No. 130), or fibrinous pericarditis (Viller's heart) (No. 135).<sup>1</sup>

In 3 animals the bones were very fragile (osteoporosis) (Nos. 111, 121, 130). One of these animals (130), however, showed also a very pronounced new-formation of bone arising from the periosteum of the extremities (especially the humerus and femur) extending out into the musculature in the form of plates, projections or broad anastomosing trabeculae. In one animal (No. 110), on the other hand, all the bones were thicker and harder than normally.

The other organs appeared macroscopically normal.

#### *Microscopic.*

Stomach: No remains seen of the mucous membrane of the fundus. No pathological cell infiltration. One animal (No. 130) showed a fairly extensive subacute ulceration (at the suture line) besides several small scars (in the cardia). The thickness of the mucous membrane seemed decreased in the cardia, increased in the pylorus.

The bone-marrow was examined microscopically in 6 of the 7 animals, not in the macroscopically normal animal (No. 134) with an observation period of only two months. In 2 animals, one with an observation period of only 5 ½ months and normal clinical findings (No. 124) and, in the spontaneously remittent case (No. 110) the bone-marrow showed a normal cell content and normal structures. In the remaining 4 animals the appearance of the bone-marrow varied somewhat. Nos. 130 and 135 presented a slight hyperplasia of the marrow in the vertebral bodies (but no cellular expansion in the marrow of the long bones of the extremities) together with marked oedema and hyperemia; one of these animals (No. 130) showed also some fibrous transformation of the bone-marrow. Nos. 111 and 121 showed marked hyperplasia with increased erythropoiesis throughout the bone-marrow system.

Central nervous system: Thorough histological examination has been carried out on 3 of the animals (Nos. 110, 111, 121). In the remaining animals a control examination was made of the spinal cord.

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<sup>1</sup> In these animals the terminal white blood count was: min. 18,880, max. 54,840, averaging 31,110 (the average value for the remaining animals, free from abscess formation, was 17,789).

In all the 5 total fundus-resected animals with a relatively long observation period (Nos. 110, 111, 121, 130, 135) and in 3 of the subtotal fundus-resected animals (Nos. 26, 45 and 46) the examination demonstrated degenerative changes in the entire central nervous system. These changes were relatively slight in the 2 last-mentioned animals, but pronounced in all the others. There was degeneration of nerve-cells, including spinal and sympathetic ganglia as well as of medullary sheaths, neuroglia reaction, and also partial hyalinization of the walls of the blood vessels. The changes were characterized by marked occurrence of swollen neurones, in all degrees. A particularly frequent phenomenon consisted in cells that were either moderately swollen, staining but faintly, almost non-granular and provided with eccentric nuclei (Nissl's »primary irritation») or markedly swollen, partly effaced, with diminished dark nuclei (Nissl's »severe ganglion cell diseases»). Necrotic cell forms were seen too, though mostly in scanty numbers. The neuronie changes have always been most pronounced in the pons, corpora quadrigemina, cerebellum and dorsal basal ganglion in the cerebrum, occurring presumably first in the pons and corpora quadrigemina. In the spinal cord the neuronie changes were moderate or marked, in particular proximally, but apparently they made their appearance later here.

Degenerative changes in the medullary sheaths were demonstrated in the spinal cord (in particular proximally) and in the medulla oblongata (in decreasing degree), localized especially to the posterior funiculi (Burdach's tract) and to the dorsal part of the lateral fasciculi.

The changes in the central nervous system have not shown any proportionality in degree to the length of the observation period, as for instance, very severe changes have been observed after a relatively short observation period (4 months) as well as after a relatively long (12 ½ months).

(The bones have not yet been examined histologically.)

Other organs: Inconstant but microscopically demonstrable changes of various nature were diagnosed in the 5 animals with the longest observation period. In the skin: subchronic inflammatory changes with marked hyperkeratosis (Nos. 110, 111, 121) or atrophy (Nos. 130, 135); in one case with oedema too (No. 121). Tongue: Slight chronic inflammatory infiltration (No. 110). Colon: Moderate, acute and chronic, ulcerative inflammation of the mucous membrane (No. 121). Certain lymph glands: Moderate or marked, acute or acute and chronic inflammation (Nos. 121 and 110, respectively), in one case associated with small abscesses (No. 111). Spleen: Slight or moderate myeloid metaplasia (cf. bone-marrow) (Nos. 121, 111); marked hemosiderosis (Nos. 130, 135), together with many megakaryocytes (No. 130). Liver: Minimal steatosis (No. 111) or slight periportal subchronic inflammation (No. 135).

### Recapitulation.

*Subtotal resection of the fundus* was performed on 8 pigs, with an observation period of 128—499, averaging 299 days. One of these animals was later employed in a therapeutic experiment. In 4 of these animals the clinical changes consisted merely in a primary transitory moderate inhibition of growth, lasting at the most for about 15 weeks, and slight anemic changes in the blood picture. In the remaining 4 animals similar changes were observed and, in addition, either symptoms of affection of the central nervous system (1 case) or emaciation and changes in the skin and hair (3 cases); in 2 of these animals, however, there was subsequently an almost complete remission.

Morphologically the animals (7) showed constantly a remnant of the fundus varying in size and in the degree of hypertrophy. In 3 of the 4 pellagrous animals the central nervous system was the site of severe or rather slight degenerative changes. In 5 of the animals, inconstant changes were observed in the form of slight, acute or chronic, inflammatory processes in the lymph glands, liver, intestines and skin.

*Total resection of the fundus* was performed on 14 pigs, with an observation period of 67—379 days, averaging 214 days. Of these animals, 7 were later employed in therapeutic experiments.

Clinically, 12 of the animals presented a moderate or severe, chronic, pellagrous picture, characterized by a varying degree — most often marked — of inhibition of growth and emaciation, changes in the skin and hair, blood and central nervous system. One animal showed a spontaneous partial remission. The changes in the blood picture in the animals with a relatively short observation period have only been inconstant, slight and varying, whereas the animals with a longer observation presented constant anemic — exceptionally, polycytemic — changes. The symptoms from the central nervous system have been severe and developed in all the 8 animals with an observation period of over 6 months. Exceptionally, a combination of pellagra and beri-beri was observed in 1 case, and a tendency to spontaneous remission in 1 case. The remaining 2 animals in this group, with a relatively short observation period, showed only insignificant clinical changes or none at all. Morphologically (7 animals) the 5 pigs with the longest observation period

(including the animal with partial remission) presented severe and extensive degenerative changes in the central nervous system, involving nerve-cells as well as medullary sheaths. In the cases examined, the bone-marrow was normal in 2 cases, slightly hyperplastic and markedly oedematous and hyperemic in 2, and markedly hyperplastic with a noticeable increase in the erythropoiesis together with myeloid metaplasia, especially in the spleen, in 2 cases; one of the animals — the one with slight hyperplasia of the bone-marrow — showed a tendency to fibrosis. A strikingly frequent feature, 4 cases, was a relatively large, circumscribed, sub-acute or subchronic inflammatory process in the lung, subcutis or pericardium. In 3 cases the bones were the site of a pronounced osteoporosis; in 1 of these cases, however, there was also a marked periosteal new-formation of bone, especially in the femora. A couple of the animals presented slight, acute or chronic inflammatory changes in the tongue, intestines or liver. In 5 of the animals with a long observation period the skin was the site of marked hyperkeratosis accompanied by inflammatory infiltration or atrophy.

In the 2 animals without pronounced clinical changes, no pathological changes were seen in the organs.

From this recapitulation it is evident that both types of operation have been able — although in a greatly different degree — to produce a pellagrous condition. After subtotal resection of the fundus this phenomenon appeared only in one-half of the animals, and here it varied somewhat, clinically and morphologically, with a tendency to remission. After total resection of the fundus, on the other hand, all the animals — with exception of the two with the shortest observation period — developed a moderate or severe, typical, chronic, progressing pellagrous symptom complex, which was subremittent but exceptionally; and this condition was characterized in particular by marked degenerative changes in the central nervous system in all the animals with a relatively long observation period.

*Comparison between the Results of Total Gastrectomy in Our Previous Experiments and Total Fundus Resection in the Present (on Pigs).*

Both types of operation have been followed by a well-characterized pellagrous symptom complex. *Qualitatively*, the clinical and morphological features have been similar after the two operations,

being characterized by changes in the weight of the animal, their state of nutrition, skin and hair, blood, bone-marrow and central nervous system. Also certain inconstant symptoms have appeared after both types of operation [osteoporosis (more frequently) and combination with beri-beri (infrequently)]. The degenerative changes in the central nervous system have been identical in type as well as in topographical distribution, in the case of nerve-cells as well as medullary sheaths, and also with regard to glia reaction.

Qualitative deviations have been recorded only from the blood and bone-marrow, differences in the dominance presented by the types of anemia or in the hyperplasia of the bone-marrow. Only total resection of the fundus has shown the particular phenomenon of a frequent occurrence of a rather large circumscribed inflammatory process in some tissue or other.

*Quantitatively*, however, the clinical picture of the condition has differed somewhat for the two types of operation. Thus, after total gastrectomy the changes in the growth, nutrition, skin and hair have constantly been marked, first progressive and then stationary. After total resection of the fundus, on the other hand, these changes have varied noticeably in intensity, being almost entirely absent in a couple of animals (those with a relatively short observation period), moderate or severe in others (all the remaining animals). A tendency to remission has been observed only in one animal on which the fundus had been resected but the remission did not involve the changes in the central nervous system. After total gastrectomy, the clinical manifestation of the changes in the central nervous system have mostly been chronic and terminally severe. After total resection of the fundus, on the other hand, these changes have terminally been either moderate or, if possible, even more severe than before; in these animals the changes did not show such a marked proportionality with the length of the observation period. In total resection of the fundus the morphological aspects of the changes was dominated by the swollen forms of cellular degeneration (Nissl's »primary irritation» and Nissl's »severe ganglion cell disease»), while sclerotic forms were relatively scarce.

Finally, differences *in the course* of the changes in the central nervous system have manifested themselves clinically. After total gastrectomy they have been increasing gradually, becoming

constant and severe after some length of time. After total resection of the fundus they usually have made their appearance soon, being very severe at once.

Owing to the quantitative differences of the changes in the animals submitted to total resection of the fundus, it would be difficult to make any comparison of the juncture for the appearance of the various pellagrous symptoms after the two types of operation. Still, the junctures for the manifestation of the changes in the central nervous system agree fairly well even though the onset is rather a little earlier after fundus resection than after gastrectomy.

### *Causation of the Gastroprival Pellagra.*

In view of the clinical and morphological identity of gastroprival pellagra with other, spontaneous or experimentally produced, pellagrous lesions in men and animals, our studies on the causation of the first-mentioned form have been based essentially on the prevailing view of pellagra as being avitaminosis B.

According to our experiments published so far, however, it appears as if the gastroprival pellagra cannot be regarded as exogenous, inasmuch as the diet of the animals has been fully sufficient, the appetite normal, and the absorption of the food has not been impeded by mechanical obstructions.

So the symptom complex has to be ascribed to endogenous disturbances, brought about primarily or secondarily by the gastrectomy. The idea suggests itself here to associate the development of this lesion with the change in the passage of the food in the intestinal canal and a resulting decrease in the absorption of vitamin B. The conditions under which the experiments were carried out have not made it possible to record the rate of the food passage roentgenographically, it is true, but administration of carbon tablets has not shown any chronological shortening of the passage on a whole; furthermore, except *sub finem*, the defecation has constantly been normal throughout the observation period.

More direct information concerning this question has been afforded by some of our therapeutic experiments, as preventive peroral administration of vitamin B preparations (in pups) and even preventive parenteral administration of vitamin B<sub>1</sub>, nicotinic acid and lactoflavin (in pigs, singly) have turned quite ineffective against the gastroprival pellagra. According to our experiences

so far, then, the condition appears hardly to be attributable to deficiency in the vitamins B mentioned, let alone an alteration of the absorption in the gastrointestinal tract.

It is justified, therefore, to attribute the development of this disease directly to the removal of the stomach itself. This view is supported indirectly by the above-mentioned conditions, directly by the following observations: 1) the constant appearance of the pellagrous changes after total gastrectomy in animals of various species, 2) the pronounced curative effect obtained by peroral administration of neutralized stomach juice, and 3) the fact that nicotinic acid — in contrast to the findings after total gastrectomy — has a curative effect on the pellagrous animals in whom merely a part of the stomach has been resected (leaving the fundus and cardia). These findings indicate that the stomach is of primary decisive significance to the development of pellagra. Accordingly, in 1936, we advanced the hypothesis that the so-called pellagrous symptom complex is due to the operative elimination of a specific antipellagrous function (factor) connected with the stomach alone. Additional support of this hypothesis was furnished by our subsequent clinic-therapeutical studies on the effect of stomach preparations on pellagrous patients who had proved refractory to treatment with vitamin B — besides by various clinical aspects of pellagrous patients advanced essentially by other authors.

Also the experiments with resection of the fundus here reported confirm our view of the primary gastrogenic character of pellagra. Thus the removal of the entire fundus has given rise to the development of a clinical picture which, except for certain minor details, shows good agreement with gastropival pellagra, while, on the other hand, the preservation of a remnant of the fundus (undergoing hypertrophy) most often has prevented the appearance of this morbid condition.

In keeping with the hypothesis advanced here, the question suggests itself to what extent each of the three regions of the stomach is of etiological significance to the development of the experimental endogenous (gastropival) pellagra and, thus, is the site of the specific antipellagrous function.

The comparison previously made between the results of total gastrectomy and total fundus resection gives some information concerning this question.

Thus the changes in the central nervous system have been just as constant after total resection of the fundus as after total gastrectomy; they have been of the same character, and they have been similar also in their chronological and topographical distribution. So the cardia and the pylorus left by the operation have not been able to prevent the development of the degenerative changes; at the most, they may have modified in part the character of the changes. Accordingly, the fundus has to be looked upon as the primarily decisive, and at any rate the most important, region of the stomach in the etiology of the endogenous degenerative changes in the central nervous system. Also the outcome of the subtotal resection of the fundus is suggestive of a certain dependency between the fundus and the appearance of the changes in the central nervous system. When this remnant of the fundus was very small, and failed to undergo secondary hypertrophy, the animal presented marked changes in the central nervous system. In most of the other cases, on the other hand, the remnant of the fundus has been able to prevent the appearance of these changes — that is, it has exceeded the required minimum of fundus capable of function. The secondary hypertrophy of the fundus remnant is to be looked upon as an expression of an increased functional demand upon the region which was greatly reduced by the operation; and the experiments with subtotal resection of the fundus illustrate that even a relatively small area of fundus is able to prevent the development of pellagra.

The fundus appears to play a prominent etiological role also in the development of the other pellagrous changes (inhibition of growth, emaciation, changes in skin and hair, besides erythropoiesis). Considering the variations in degrees presented by the mentioned pellagrous symptoms after total resection of the fundus (in contrast to the findings after total gastrectomy, where the changes constantly were severe) the cardia and pylorus appear to possess a certain (secondary?) antipellagrous function against these symptoms.

According to our clinic-therapeutic studies recently published (Petri and collaborators, 1941), in pigs submitted to total resection of the fundus as well as to total gastrectomy, the liver is lacking completely the antipernicious anemic principle when the animals have been observed for 8 months or more. The liver extracts were



prepared from Swine 110, 111, 118, 124. When pigs after resection of the fundus are given nicotinic acid for some months the liver may again be brought to contain the active principle. From these findings we have drawn the conclusion that the fundus is that region of the gastric mucosa which is primarily decisive of the formation of the active liver principle, and that the two other regions of the stomach play a certain, secondary role in this respect.

From these previous investigations as well as from the present experiments with total resection of the fundus, it is evident, then, that there exists a primary etiological relation between the fundus of the stomach and the appearance of the pellagrous changes in the central nervous system together with the disappearance (cessation of production) of the active liver principle. Presumably, a certain secondary etiological significance is to be assigned to the cardia and pylorus, at any rate with regard to the formation of the active liver principle.

### Summary.

Attempts are made experimentally to elucidate the etiological significance of the fundus region by means of elective operations with subtotal or total resection of the fundus on respectively 8 and 14 pigs, with an average observation period of 299 and 214 days respectively.

In half of the animals submitted to subtotal resection of the fundus there developed clinically and morphologically a lesion of the central nervous system or a pellagrous condition, in part with morphological changes in the central nervous system.

In all the animals submitted to total resection of the fundus, excepting two with a relatively short observation period, there developed a moderate or severe, chronic, neurocutaneous symptom complex («experimental endogenous pellagra»), characterized especially by severe degenerative changes in the central nervous system.

A detailed account is given of the clinical and morphological changes observed after both types of operation. Further, the results of total fundus resection are compared to the results in our previous experiments with total gastrectomy.

The causation of the experimental «gastroprival» pellagra is discussed. The hypothesis advanced by us (1936), about the stomach being of primary decisive importance to the development

of pellagra (specific antipellagrous function) has been confirmed by the experiments with resection of the fundus. For these experiments show that *the fundus is that region within the stomach which is primarily decisive as to the development of the pellagrous degenerative changes in the central nervous system* (and also — according to our previous investigations — to the formation of the antipernicious-anemic principle).

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## Untersuchungen über das Diaminoxydaseferment („Histaminase“).

Von .

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Das Vorkommen eines katalytischen Systems, welches Histamin zu spalten vermag, ist von Best 1929 nachgewiesen worden. Es wurde als »Histaminase« bezeichnet. Seitdem hat man dieses System und die Reaktion, welche beim Abbau des Histamins stattfindet, eingehend studiert. Anfangs wollte man geltend machen, dass es sich um ein einheitliches Ferment, die »Histaminase«, handle; man fand aber bald, dass der Abbau des Histamins in mehreren Etappen vonstatten geht: Desaminierung der Seitenkette, Sprengung des Imidazolringes und Desaminierung desselben, weshalb man triftige Gründe zu der Annahme hatte, dass beim vollständigen Abbau des Histamins mehrere Ferment-systeme beteiligt seien. Ferner erwies sich die ursprüngliche »Histaminase« als nicht spezifisch, sie vermochte vielmehr auch die oxydative Desaminierung einer Reihe anderer Diamine, wie Äthylendiamin, Putreszin, Kadaverin, Agmatin, Spermin (Zeller, 1938), zu katalysieren. Man hatte es demnach mit einer Diaminoxydase zu tun. In einer persönlichen Mitteilung an Zeller (1938) hat Mc Henry das den Imidazolring öffnende Fermentsystem als »Histaminase im engeren Sinne« bezeichnet. Während der letzten Jahre richtete sich das Interesse auf das Studium der Diamin-

oxydase (Zeller u. Mitarb.). Durch Untersuchung der Hemmbarkeit des Fermentes, insbesondere der Zyanhemmbarkeit, wurde man zunächst zu der Ansicht veranlasst, es handle sich um ein Häminprotein. Da aber die Zyanhemmung niemals vollständig oder konstant war, und sich keine Hemmung durch CO oder Natriumphosphat ergab (Gebauer-Fuelnegg, 1932), wurde diese Theorie aufgegeben. Aus Arbeiten von Zeller geht hervor, dass die prosthetische Gruppe eine Karbonylgruppe enthalten muss und wahrscheinlich Flavinkonstitution hat (Zeller, 1940).

Angaben über Reinigungsversuche der »Histaminase« oder Diaminoxidase sind im Schrifttum sehr spärlich. Die meisten Autoren haben Bests Anweisungen befolgt und haben gemahlene Niere mit Azeton behandelt und aus dem getrockneten Azetonpulver einen aktiven wässrigen oder Glyzerinextrakt hergestellt. — Es wurden dann Versuche angestellt, das aktive Prinzip aus diesem wässrigen Extrakt zu gewinnen und durch Adsorption an eine grosse Anzahl verschiedener Substanzen, sowie auch durch Fraktionierung mit Ammoniumsulfat, Azeton und Pikrinsäure anzureichern (Best u. Mc Henry, 1930; Mc Henry u. Gavin, 1931, 1935; Edlbacher u. Zeller, 1937; Kiese, 1940). Es ist indessen sehr schwer, sich an Hand des Schrifttums eine sichere Auffassung über die Aktivität der erhaltenen Präparate zu bilden, was einerseits darauf beruht, dass die Autoren hierüber nichts angegeben haben, und andererseits darauf, dass fast jeder Autor seine eigene Standardisierungsmethode angewendet hat. Das im allgemeinen bei biologischen Versuchen verwendete Präparat enthielt eine Histaminaseeinheit pro 100 mg Präparatsubstanz. Die Histaminaseeinheit wird als diejenige Menge wirksames Ferment definiert, welche binnen 24 Stunden bei 37° 1 mg Histaminbase in Phosphatpuffer bei pH 7.0 zu inaktivieren vermag.

Das bei der vorliegenden Arbeit verfolgte Ziel war, ein Fermentpräparat mit grösstmöglicher histaminspaltender Aktivität darzustellen. Dazu wurde das Ferment gewählt, welches die erste Oxydationsphase beim Abbau des Histaminmoleküls katalysiert, während der die Seitenkette desaminiert wird (Zeller). Eine Desaminierung der Seitenkette verursacht eine durchgreifende, sowohl quantitative wie qualitative Veränderung der biologischen Aktivität (Best u. Mc Henry, 1930; Guggenheim, 1940).

*Standardisierung.*

Mehrere biologische Diamine, unter diesen Histamin, werden stufenweise oxydiert. Das Wahrscheinliche ist, dass jede Stufe von ihrem Ferment katalysiert wird. Beim Studium der Oxydation des Histaminmoleküls in der Warburgschen Apparatur findet man, dass der Sauerstoffverbrauch nach einer kurzen Latenzzeit mit konstanter Geschwindigkeit verläuft, bis ein halbes Molekül Sauerstoff verbraucht ist, worauf die Geschwindigkeit plötzlich abnimmt, aber dann weiterhin konstant bleibt. Bei den Standardisierungen wurde der Sauerstoffverbrauch während der ersten Periode der Reaktion als Indikator für die Fermentaktivität verwendet (Zeller, 1939).

Die Temperatur des Wasserbades betrug 38°. In der Hauptkammer des Warburggefässes befanden sich 2.0 ml m/15 Phosphatpuffer  $p_{\text{H}}$  7.7 und 1.2 ml Fermentlösung, im »Anhang« 0.1 ml Histaminlösung, 0.5 mg Histamindihydrochlorid entsprechend. Die Endkonzentration des Histamins in der Reaktionsmischung wurde demnach  $0.9 \cdot 10^{-3}$  m. Der »Einsatz« enthielt 0.2 ml 50 %ige  $\text{H}_2\text{SO}_4$ . Die Schüttelgeschwindigkeit war 75 Schläge pro Min. Als Einheit wurde die von Zeller eingeführte DoE verwendet, worunter die Aktivität zu verstehen ist, welche eine Anfangsgeschwindigkeit der Reaktion von  $10^{-6}$  Mol pro Stunde umgewandelt zustande bringt. Da die Geschwindigkeit bei der Umwandlung von Kadaverin 1.3 mal so gross ist wie bei Histamin, muss eins von beiden konsequent angewendet werden. Bei den vorliegenden Untersuchungen wurde stets Histamin in Form von Histamindihydrochlorid verwendet.

*Präparierung.*

In einem gewöhnlichen Fleischwolf wurden 800 g frische, gereinigte Schweineniere zweimal gemahlen. Der Nierenbrei wurde dann mit 200 ml m/15 Phosphatpuffer  $p_{\text{H}}$  7.7 versetzt und durch ein Filtriertuch gepresst. Der Extrakt, 460 ml, wurde durch Zusatz von 230 ml gesätt.  $\text{Am}_2\text{SO}_4$ -Lösung gefällt. Der Niederschlag wurde abzentrifugiert, und es liess sich eine klare rote Mutterlauge abpipettieren. Diese, deren Volumen 260 ml betrug, wurde mit 260 ml gesätt.  $\text{Am}_2\text{SO}_4$ -Lösung versetzt, eine Stunde

gemischt, worauf der Niederschlag auf einem gewöhnlichen Filter in Zimmertemperatur über Nacht abfiltriert wurde. Der halbtrockene Niederschlag wurde in der kleinstmöglichen Menge Aqu. dest., welchem 5n Ammoniak auf  $p_H$  7.5 gebracht wurde, wiedergelöst. Die Lösung wurde durch Zentrifugieren von Filtrierpapierresten gereinigt. Dann wurde sie bei  $+5^\circ$  über Nacht mit physiol. Kochsalzlösung dialysiert, wonach bei Zimmertemperatur eine Dialyse mit Aqu. dest. ausgeführt wurde. Das Dialysat wurde unter Umrühren 10 Min. lang auf  $+50^\circ$  erwärmt. Ein graubrauner Niederschlag wurde abzentrifugiert. Das Volumen des Dialysats nach der Erwärmung betrug 108 ml. Dieses wurde mit 54 ml gesätt.  $Am_2SO_4$ -Lösung versetzt. Ein geringfügiger Niederschlag wurde abzentrifugiert. Das Dekantat wurde dann mit 162 ml gesätt.  $Am_2SO_4$ -Lösung gefällt. Der entstehende Niederschlag, welcher sich leicht abzentrifugieren liess, wurde im kleinstmöglichen Volumen m/100 Phosphatpuffer  $p_H$  7.5 gelöst und durch Dialyse bei  $+5^\circ$  über Nacht von  $Am_2SO_4$  gereinigt. Das Volumen war nach der Dialyse 145 ml. Die Schweineniere enthielt 5 DoE pro g und die Endkonzentration 175 DoE pro g, weshalb die Reinigung 35:1 ausmachte. Die gesamte Ausgangsaktivität war 4000 DoE und die des Präparats 350 DoE. Die Ausbeute betrug demnach 8.7 %.

### Elektrophorese.

Bei diesen Untersuchungen wurde ein von Theorell (1934) konstruierter Elektrophoreseapparat verwendet.

*Elektrophorese 1.* Temperatur des Wasserbades:  $20^\circ$ . Es wurde das oben beschriebene Präparat verwendet.  $p_H$  7.52. Elektrolyt. Leitfähigkeit:  $3.3 \cdot 10^{-3}$  rec. Ohm. Stromstärke:  $5 \cdot 10^{-3}$  Amp. Zeit: 5 Stunden = 18,000 Sekunden. Der Inhalt der Zellen wurde in der oben angegebenen Weise hinsichtlich des aktiven Prinzips analysiert.

Resultat: Das aktive Prinzip wanderte mit folgender Geschwindigkeit zur Anode:  $u = 4.55 \cdot 10^{-5}$ .

*Elektrophorese 2.* Temperatur des Wasserbades:  $20^\circ$ . Es wurde dasselbe Präparat wie oben verwendet.  $p_H$  7.83. Elektrolyt. Leitfähigkeit:  $3.38 \cdot 10^{-3}$  rec. Ohm. Stromstärke:  $5 \cdot 10^{-3}$  Amp. Zeit: 5 Stunden 35 Min. Nach 2 Stunden 35 Min. wurde die Wanderung dadurch kompensiert, dass 15 ml Puffer in das Anodengefäss

hineinpipettiert wurden, was einer Verschiebung der Höhe des Flüssigkeitspfeilers im U-Röhrchen des Elektrophoreseapparats um 3.75 cm entspricht. Der Inhalt der Zellen wurde quantitativ mit Bezug auf Aktivität und organisches Trockengewicht, sowie qualitativ hinsichtlich des Vorkommens von Flavinprotein (Luminoflavin nach Warburg u. Christian, 1938) und Häminprotein (spektroskopische Untersuchung der Lichtabsorption bei 630  $m\mu$ ) analysiert.

Nach Beendigung der Elektrophorese war die Lösung in drei Schichten geteilt. Im Anodenteil des U-Röhrchens war sie nahezu farblos, aber opaleszent, im Kathodenteil braunrot und klar und im Zwischenstück eine Mischung von beiden. Der Zelleninhalt der Anodenseite gab eine stark positive Luminoflavinreaktion, ebenso derjenige der Bodenzelle, nicht aber der Inhalt der drei obersten Kathodenzellen, welcher stattdessen ein starkes Hämatinspektrum aufwies. Die Standardisierungen ergaben, dass das aktive Prinzip mit der Luminoflavinreaktion, nicht mit dem Hämatin, Hand in Hand ging. Bei der Elektrophorese wurde eine Reinigung erzielt, indem der Inhalt der obersten Zelle der Anodenseite 620 DoE pro g organisches Trockengewicht enthielt, während die ursprüngliche Lösung 175 DoE pro g organisches Trockengewicht enthalten hatte. Die endgültige Reinigung betrug also 124:1.

### *Erörterung der Resultate.*

Verf. hat umfangreiche Versuche angestellt, um die Diaminoxidase durch Adsorption und Elution zu reinigen. Diese sind aber sämtlich misslungen, und zwar infolge der Schwierigkeit, das Ferment zu eluieren, welches äusserst labil zu sein und leicht inaktiviert zu werden scheint. Das Ferment ist gegen saure Reaktion empfindlich. Bei den Präparierungen wurde nie unter pH 7 heruntergegangen. Der grösste Teil der Aktivität fällt zwischen  $\frac{1}{3}$  und  $\frac{2}{3}$  Sättigung mit Ammoniumsulfat, worauf auch Kiese (1940) hingewiesen hat. Durch Wärmebehandlung des Präparats wurde eine wesentlich gesteigerte Haltbarkeit der Fermentlösungen erreicht. Dieselben konnten monatelang bei  $-10^\circ$  aufbewahrt werden, ohne dass die Aktivität nachliess.

Die elektrophoretische Untersuchung, die nur als eine Orientierung aufzufassen ist, zeigte, dass das aktive Prinzip von einer

Häminproteinfraktion getrennt werden konnte, und dass es einer Flavinproteinfraktion folgte. Da das Ferment noch nicht isoliert ist, ist es indessen unmöglich, sich über die Konstitution desselben mit Bestimmtheit zu äussern. Aus Zellers und Verfs. Arbeiten dürfte jedoch hervorgehen, dass die Diaminoxydase wahrscheinlich ein Flavoprotein ist.

Die Aktivität des Fermentpräparats des Verfs. entspricht 620 DoE pro g organische Trockensubstanz oder 2740 Histaminase-einheiten pro g organische Trockensubstanz.

### Zusammenfassung.

Durch fraktionierte Ammoniumsulfat-Fällung und Elektrophorese erhielt Verf. ein Diaminoxydase- (Histaminase-) Präparat mit hoher Aktivität.

Die Diaminoxydase dürfte ein Flavoprotein sein.

(Die vorliegende Untersuchung wurde durch Subvention seitens der Stiftung »Johan och Thérèse Anderssons Minne« ermöglicht.)

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*Eberhard Koch*: Allgemeine Eektrokardiographie. Mit einem Anhang: Richtlinien für die Auswertung eines Ekg von Elsbeth Koch-Momm. 7., neu bearbeitete Auflage. 56 S. 47 Abb. Preis: geh. RM 2.25. Verlag von Theodor Steinkopff, Dresden und Leipzig, 1943.

*Åke Edlén*: Wachstum und Milieu bei *Daphnia magna*. Experimentelle Untersuchungen über den Einfluss von Licht und Dunkel auf Wachstum und Lebenslauf. 125 S. 36 Abb. A.-B, Gleerupska Univ.-Bokhandeln, Lund, 1943.

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(From the Laboratory for the Theory of Gymnastics, University of Copenhagen).

## Effects of ultra-violet rays in depth and duration.

By

H. I. BING.

(Submitted for publication February 18, 1943).

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When, at the end of the nineteenth century, carbon-arc lamp light, based on Finsen's observations, was included in medical treatment, the ultra-violet rays were soon recognised as being the most effective rays. Experiments were performed to find a substitute for the costly carbon-arc lamp light, which could radiate ultra-violet rays, be less expensive, and more adaptable. Among the sources investigated, *mercury quartz light* was found to be the best, although it was not universally recognised as being equally effective as rays from carbon-arc lamps. Ultra-violet ray treatment is used both as a local cure for skin affections, and as »light baths» for different internal diseases. In the former case, it has been relatively easier to approach a determination of the effect of rays on the skin.

In view of the enormous use to which light treatment has been put, it is astonishing how little has been done to investigate its biological effects.

The anti-rachitic effect of light is well understood, but otherwise, positive results of treatment have merely been recorded, mostly without closer investigation. Some experiments explaining

the general effect of light have, however, been carried out, among which I shall mention the much-quoted experiments of Hasselbalch (1905), who found that respiration after ultra-violet ray treatment became slower and deeper. Sonne (1919), investigated the effect of mixed rays on the blood, and thought the visible rays most effective. Experiments on animals, by Gassul (1919), Levy (1916, 1919), v. Reis and Sjøstrand (1928), investigated the distribution of blood in the parenchymatous organs after ray treatment and found an increase in blood volume.

I became interested in this problem, partly by observing that ultra-violet ray exposure of the thorax gave rise to an enlargement of the lung under the treated regions, and partly, because I had seen beneficial effects of light in cases of rheumatic muscular affections.

On hearing that Buchthal, Honke and Lindhard were experimenting with intra-muscular temperature under varying physiological conditions, a possibility of testing my theories experimentally, presented itself. I approached Dr. Buchthal who kindly allowed me the benefit of his experience.

In the course of the present investigation, the work of O. Lippross (1942), came to my notice. He examined the temperature of different tissues under many different conditions after ray treatment among others and found here that there was a rise in temperature in the deeper tissues some time after treatment had stopped, which could continue for the 100 minutes the observation lasted.

In the present experiments, I have not examined the immediate effect, but have repeatedly observed the temperature of the treated muscle during several days, and, as control, measured the temperature in the corresponding untreated muscle on the other side. Measurements are performed thermo-electrically, the one thermojunction being placed in the hypodermic canula which is introduced into the tissue, the other in a Dewar-vessel, with constant temperature. With this arrangement the temperature can be measured with an exactitude of less than  $1/10^{\circ}\text{C}$ .

According to unpublished experiments by Buchthal, Honke and Lindhard, the temperature in the resting muscle is between  $34^{\circ}$  and  $36^{\circ}$ . It rises if the muscle performs work. This low temperature level is confirmed in the m.biceps of my experimental subjects.

Table I.

All measurements are quoted in the first Experiments only the average in the other experiments.

I. 9/11 Measurement in untreated m.biceps dext.

distal.....	36.0	
	35.9	
	35.8	35.9
	35.8	
	35.8	
proximal..	36.3	
	36.3	36.3
	36.3	

11/11 Measurement in untreated m.biceps dext

distal ....	35.1	
	35.1	35.1
	35.0	
proximal..	35.9	
	35.6	35.6
	35.2	

Measurements are performed in the distal and proximal part of the muscle. In later experiments the junction was placed in two distal regions. The experimental subjects had usually not been sufficiently long at rest to insure standard conditions, and to exclude certain irregularities, due to previous movements of the arms, though a resting period of about 30 minutes preceded the experiments. When comparing the treated and untreated muscles by measuring alternately medially and laterally in the respective muscles, this irregularity does not affect the experimental results.

The experiment was carried out in the following way:

Every morning, for from one to three days, a certain area of the skin over a/m. biceps was treated with ultra-violet rays, at a distance of 20 cm for 2 to 3 minutes. A few hours later, the first intra-muscular temperature was determined on the treated and untreated sides.

From the table and the figure, it is seen that the intra-muscular temperature is higher on the side where the skin has been treated. This increase lasts for some days after radiation has ceased. In the last experiment, the increase lasted for three days after the final treatment. Here the most considerable difference found in temperature amounted to about 2°C.

Table II.

Treatment of right upper arm 12/11 13/11 14/11 9 a. m.

II <sup>1</sup>	14/11	Measurement of treated right arm 4 p. m.	Measurement of untreated left arm.
	proximal..	36.9	proximal 36.2
		36.9 36.8	36.1 36.1
		36.7	36.0
	distal ....	36.9	36.0
		36.9	distal .. 36.1
		36.9 36.9	36.1 35.9
		36.8	35.0

III. Treatment of right upper arm 21/11 22/11 23/11 24/11 7 a. m.

23/11	4 p. m.	Measurement of treated and untreated arm	
		Treated arm	Untreated arm.
		36.67	35.06
24/11		37.02	36.10
25/11		36.19	36.30
26/11		36.62	36.29

IV. Treatment of left upper arm 28/11 30/11 1/12 8.45 a.m.

1/12 4 p.m.	37.20	36.24
3/12	36.82	36.22
4/12	36.52	36.32

V. Treatment of left upper arm 7/12 and 8/12, 6.45 a.m.

7/12 3 p.m.	36.19	35.57
8/12 4 p.m.	36.58	34.62
9/12	36.40	35.09
10/12	36.87	35.82
11/12	36.12	35.16
12/12	36.15	37.75

What is the explanation of this protracted increase in temperature after radiating with ultra-violet rays? One might suppose that heat is led from the erythema of the skin to the deeper tissues. This, however, is improbable. In experiment No. 2, the temperature was measured subcutaneously on both sides. On the second day, the temperature on the treated side was 35.4°, and on the other side 36.1°, i.e. the temperature beyond the erythema was lower than that measured intra-muscularly.

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<sup>1</sup> Same person as in I.

There is a possibility of either a humoral or a reflex initiation of this increase in temperature in the muscle. One theory is that universal effect is due to substances which are formed in the skin, and re-absorbed from it. On the other hand, a reflex effect, dilating the vessels in the muscle, is more probable. The higher temperature would then be caused by the increased flow of blood. This agrees

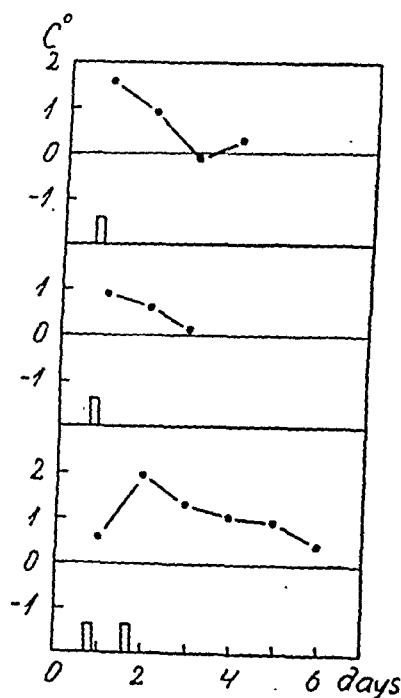


Fig. 1. Difference in intra-muscular temperature between an ultra-violet ray treated and an untreated arm.  
 abscissa: days after treatment.  
 ordinate: difference in temperature in C.  
 The pillar indicates light treatment.

with the previously mentioned investigations of Gassul (1919) Levy (1916, 1919), v. Reis and Sjöstrand (1938), who, using various methods, found a large amount of blood in the internal organs after ray treatment. Besides this, v. Reis and Sjöstrand showed that this increase did not occur if the nerve supply to the skin was interrupted. The observation is furthermore in agreement with the reflectory enlargement of the lungs occurring after radiation of the skin of the thorax. [Bing (1936)].

The result of the present experiment which shows increase in intra-muscular temperature, even long after the ultra violet ray

treatment has ceased, may contribute to the explanation of its beneficial effects on rheumatic muscular affections. The present experiments permit us to draw only very careful conclusions, but they may help to penetrate the mystery which surrounds the beneficial effect of »light baths».

### Resumé.

The intra-muscular temperature is examined after radiation of a certain area of the skin over the muscle by ultra-violet rays.

In the underlying muscle, the temperature is measured thermoelectrically by inserting a thermo-junction. The intra-muscular temperature of the side treated with ultra-violet rays increases, and keeps at this level for several days after treatment.

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## Kreislaufstörungen bei Krampfanfällen epileptischen Typs.

### III. Das Elektrokardiogramm beim Elektroschock.

Von

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(Bei der Redaktion am 19. Januar 1943 eingegangen).

In der vorliegenden Serie von Untersuchungen über die Kreislaufsphysiologie des Krampfanfalls ist bereits früher (Gord und Silfverskiöld 1943, Silfverskiöld und Åmark 1943) angegeben worden, dass man beim klinischen Elektroschock ein Bild erhält, welches an die Verhältnisse beim Valsalvaschen Versuch erinnert. Der intraabdominale Druck steigt sehr stark, und der intrathorakale erreicht oft hohe Werte. Hand in Hand damit geht eine Drucksteigerung in Arterien, Venen und Liquorräumen, und ferner scheint im Zusammenhang mit der Abnahme des Schlagvolumens der Blutstrom zur Peripherie eine Beeinträchtigung zu erfahren.

In einer Arbeit von Streit (1941), über welche unten des näheren berichtet werden wird, werden Ekgveränderungen nach Elektroschock beschrieben. Diese erinnern in gewissen Beziehungen an die Beobachtungen bei spontanen epileptischen Anfällen sowie beim Cardiazolschock, in einigen Punkten aber auch an das Arbeits-ekg. Gewisse gemeinsame Züge scheinen also das Ekg bei Krampfanfällen epileptischen Typs, gleichgültig welcher Ätiologie, zu kennzeichnen. So konstatierten Hadorn und Tillmann (1935) unmittelbar nach epileptischen Anfällen Ekgveränderungen derjenigen Art, wie sie im Arbeits-ekg gewöhnlich sind: eine relativ rasch



vorübergehende Höhenzunahme der T-Zacken. Diese Autoren bezeichnen auch den Krampfanfall als den adäquaten »Arbeitsversuch« für den Epileptiker.

Das Ekg nach *Cardiazolschock* ist u.a. von Hadorn (1937) studiert worden, der eine beträchtliche Tachykardie sowie oft eine Senkung der S-T-Strecke, im Verein mit Höherwerden der T-Zacke, feststellte. Ausserdem fand er häufig Vorhoffstörungen, wie Reizleitungsveränderungen, Extrasystolen und in vereinzelt Fällen auch Vorhofflimmern. Hingegen hat H. laut Angabe nach *Cardiazolschock* nicht die seiner Ansicht nach für den Insulinschock typischen Dauererscheinungen von Herzmuskelschädigung in Form von Senkung des Zwischenstücks usw. beobachtet.

Géraudel (1938) konnte nach *Cardiazolschock* keine größeren Veränderungen des Ekgs konstatieren, bemerkte aber in grossem Umfang neben der Tachykardie noch eine Höhenzunahme und Formveränderung der P- und T-Zacken, besonders markant in Ableitung 2 und 3. Die Befunde wechselten allerdings von Fall zu Fall recht stark.

Regnér und Ewert (1939) sahen bei 10 Fällen von Schizophrenie nach *Cardiazolschock* zunächst abwechselnd eine Vergrösserung und Verkleinerung der T-Zacken. Auf eine Erhöhung über den Ausgangswert hinaus folgte regelmässig eine oft anhaltende und gewöhnlich von einer Senkung der S-T-Strecke begleitete Abflachung. Diese Veränderung liess sich in gewissen Fällen noch 2 Stunden nach dem Schock feststellen.

Streit (1941) war der erste, welcher das Ekg im Zusammenhang mit dem *Elektroschock* zum Gegenstand einer Untersuchung grösseren Massstabs gemacht hat. Sein Material bestand aus rund 40 Patienten, grösstenteils ältern Schizophreniefällen. Unmittelbar nach dem Schock wurde durchweg Sinustachykardie bis zur Schlagzahl 250 während 1—4 Minuten beobachtet. Vorhofflimmern kam nicht vor. Man fand 3—4 Minuten nach Schluss des Krampfs in gewissen Fällen Extrasystolen. Regelmässig nahm die Höhe der P-Zacken nach dem Krampf zu; dies war namentlich bei P<sub>2</sub> der Fall. Der QRS-Komplex wies wechselnde Veränderungen auf, u.a. sowohl Erhöhung wie Abflachung der R-Zacke. Das Verhalten von R<sub>1</sub> war jedoch bemerkenswert einheitlich, nämlich Senkung in 30 von 35 Fällen. In allen Ableitungen wurden die T-Zacken wie nach spontanen epileptischen Anfällen höher. Nach

einigen Minuten wurde diese Veränderung von einer markanten Verflachung abgelöst, die bei  $T_1$  am wenigsten, bei  $T_3$  am meisten ausgeprägt war. Die S-T-Strecke war in ca.  $\frac{1}{4}$  der Fälle gesenkt; diese Veränderung blieb indessen nicht länger als 1 Stunde bestehen. Oft wurden U-Wellen beobachtet. Beim Abortivschock sank die Herzfrequenz in der Regel um 10—20 Schläge pro Minute. Bei einigen dieser Fälle kam es sogar zu langdauerndem Herzstillstand, bei dem S. einige äusserst bedrohliche Zustände mit »Schaum vor den Lippen« und »Gesichtsfarbe schwarzblau« beschreibt.

Holzer und Polzer (1941) fanden im Ekg nach Elektroschock regelmässig Sinustachykardie, P pulmonale und Koronarinsuffizienz rechts. Ihrer Ansicht nach gleichen die Veränderungen im Prinzip denen beim chemisch ausgelösten Schock, nur sind sie weniger ausgesprochen als bei letzterem. Die Koronarinsuffizienz der rechten Herzhälfte besitzt Interesse, da sie scheinbar mit einer Behauptung im Einklang steht, welche im Schrifttum über das Ekg bei spontaner Epilepsie grosse Verbreitung gefunden hat. In diesem hatte man früher, zum Teil auf Obduktionsbefunde und Ergebnisse von Tierversuchen gestützt, geltend machen wollen, die Epilepsie habe eine fortschreitende Koronarinsuffizienz zur Folge, und zwar deshalb, weil ein Koronarspasmus eine Komponente des Krampfanfalls bilden soll. Gegen diese Behauptung haben indessen Hadorn und Tillmann (1935) eine sehr wohlbegründete Kritik gerichtet. Der Wert der Arbeit von Holzer und Polzer wird durch erhebliche Irrtümer ihrer allgemeinen Anschauungen über den Elektroschock verringert.

Allerdings kommt es auch nach dem *Valsalvaschen Versuch* zu beträchtlichen Veränderungen im Ekg. Mithin lag der Versuch nahe, die Ekgbefunde nach Elektrokrampf und Valsalvaschem Versuch des näheren miteinander zu vergleichen, in der Absicht, zu vermehrten Erfahrungen hinsichtlich des einleitend angestellten Vergleichs zwischen den Zirkulationsbedingungen bei diesen beiden Zuständen zu gelangen.

Das Ekg beim Valsalvaschen Versuch ist zuerst von Kahn (1909) beschrieben worden. Ein mehr ins einzelne gehendes Studium wurde von Bürger (1921, 1925, 1926) durchgeführt, der auf dem Standpunkt steht, es liessen sich charakteristische Veränderungen durchaus nicht immer nachweisen. Die postpressorische Brady-

kardie, welche natürlich schon vorher bekannt gewesen war, kann nach Bürger von Extrasystolen, evtl. in Form frustraner Kontraktionen, verdeckt werden, während markantere Arrhythmien in diesem Stadium auf präformierte Myokardschädigungen hindeuten sollen. In seiner letzten Arbeit (1926) fasst Bürger gewisse Hauptkennzeichen für das pressorische Stadium zusammen: verkürzte Herzpause, gesteigerte Höhe der P-Zacken, Änderung des QRS-Komplexes, Verkleinerung der T-Zacken. Keiner dieser Befunde kam jedoch ausnahmslos vor. Postpressorisch kann die P-Zacke gänzlich verschwinden, der P-R-Abstand grösser werden und einzelne Systolen ausfallen. Ferner kommen hin und wieder atrioventrikuläre Extrasystolen, wandernde P-Zacken und Dissoziation zwischen Vorhof und Kammer zustande. Das Bild lässt sich nach B. am besten im Sinne einer pressorischen Accelerans- und postpressorischen Vagusdominanz deuten. Ganz konstant vorkommende Veränderungen im postpressorischen Stadium scheinen nach Bürger nicht zu existieren.

Nordenfelt (1934) konstatierte eine Senkung von  $T_2$  während der pressorischen Phase des Valsalvaschen Versuchs sowie in einem Falle ausserdem Inversion der ganzen Kurve in Ableitung 1, was als Folge der durch den Druck verursachten, einen Situs inversus nachahmenden Verschiebung des Herzens aufgefasst wurde.

Ein sehr grosses Ekgmaterial hat Borst (1935) bearbeitet, der bei 400 Untersuchungen während und nach dem Valsalvaschen Versuch eine ganze Reihe verschiedener Veränderungen beobachtete. Insgesamt wurden Störungen in ca. 20 % des Materials entdeckt. Diese bestanden einmal in pressorischer Vorhofpfropfung und verändertem Reizursprung sowie Extrasystolen, sodann in postpressorischen Reizleitungsstörungen und Änderung des Reizursprungs auch in diesem Stadium. Über markante und durchweg auftretende Veränderungen der Höhe der einzelnen Zacken wird nicht berichtet.

Schlomka und Lammert (1935) fanden im grossen ganzen dasselbe wie Bürger, meinen aber ausserdem regelmässig eine Verschiebung des Quotienten  $\frac{\text{Höhe der S-Zacke}}{\text{Höhe der R-Zacke}}$  festgestellt zu haben, indem dieser sich dem Wert 1 näherte oder denselben unterschritt.

Es ist indessen von vornherein darauf hinzuweisen, dass bei einem Valsalvaschen Versuch diejenige Druckhöhe nie erreicht werden kann, mit welcher wir es in einem Krampfanfall während des Elektroschocks zu tun haben. Wir rechnen damit, dass sich in der tonischen Phase des Elektrokrampfs bei jüngeren Männern für 10—15 Sekunden ein intraabdominaler Druck von über 200 mm Hg und ein intrathorakaler von mehr als 100 mm Hg erzielen lässt. Im Laufe von ca. 30 Sekunden kehrt dann der Druck in den grossen Körperhöhlen zu den Ausgangswerten zurück. Beim Valsalvaschen Versuch können derartige Individuen vielleicht einen intrathorakalen Druck von 60 mm Hg  $\frac{1}{2}$  Minute lang aufrechterhalten; der Druck in der Bauchhöhle ist hierbei ungefähr ebenso hoch. Bei den im folgenden beschriebenen Untersuchungen waren die Versuchspersonen beim Valsalvaschen Versuch kräftige jüngere Männer, während die Wirkungen des Elektrokrampfs grösstenteils an weiblichen Kranken studiert wurden; hierdurch wurde der Druckunterschied zwischen den beiden Serien reduziert und die Vergleichbarkeit derselben vielleicht gesteigert.

Ferner sei in diesem Zusammenhang noch hervorgehoben, dass das Elektroschockmaterial einige ältere Frauen enthält, bei denen der Verdacht auf eine gewisse Minderwertigkeit des Myokards nicht unbedingt von der Hand zu weisen war, wenn auch das Ekg vor der Schockbehandlung keinerlei Anhaltspunkte für sichere pathologische Veränderungen im Sinne der üblichen Deutungsweise ergeben hatte. Wir haben indessen weder in der vorliegenden Versuchsreihe noch auch überhaupt jemals bei dem umfassenden Gesamtmaterial der Psychiatrischen Klinik so beunruhigende Zwischenfälle wie die von Streit beschriebenen gesehen. Dies kann darauf zurückzuführen sein, dass sich unter den von S. untersuchten Personen mehr solche mit pathologisch veränderten Herzen befunden haben als in unserm Material; die Ursache kann aber auch die sein, dass unsere Kranken während einiger Minuten vor dem Schock regelmässig Sauerstoffinhalationen erhalten haben.

### *Methodik*

*Valsalvascher Versuch:* Das Material besteht aus 13 gesunden Männern mit kräftigem Körperbau im Alter 23—30 Jahre. Die Versuchspersonen mussten nach 10 tiefen Atemzügen 30 Sekunden

lang gegen ein Anaeroidmanometer ausatmen, wobei der Druck bei 40—60 mm Hg gehalten werden konnte. Sämtliche Versuche wurden in liegender Stellung vorgenommen; Kollapse wurden nicht beobachtet. Elektrokardiogramme wurden mit der Apparatur von Siemens in 4 Ableitungen unmittelbar vor, während und unmittelbar nach dem Versuch sowie 1 und 5 Minuten nach Schluss desselben aufgenommen.

*Elektroschock:* Das Material enthält 13 Kranke aus der Klinik im Alter 17—57 Jahre. Von diesen waren 5 über 50 Jahre, 2 zwischen 40 und 50, 3 zwischen 30 und 40 sowie 2 im Alter 20—30 Jahre; 11 waren Frauen, 2 Männer. Sie waren sämtlich anamnestisch und klinisch herzgesund. Das Ekg vor dem Schock wies bei keinem der Fälle sichere pathologische Veränderungen auf.

Das Verfahren bei der Schockbehandlung entsprach in allen Punkten der in der Psychiatrischen Klinik gebräuchlichen Routine. Hier sei noch einmal betont, dass wir der einige Minuten dauernden Sauerstoffinhalation vor dem Schock Bedeutung für die Verhinderung einer Asphyxie während des letzteren zuschreiben. Unsere Resultate können infolgedessen vielleicht nicht ohne weiteres mit denen älterer Untersucher verglichen werden, in deren Material Asphyxie vorgekommen sein dürfte.

Elektrokardiogramme wurden beim Elektroschock mit derselben Apparatur wie beim Valsalvaschen Versuch in 4 Ableitungen und in der Reihenfolge: unmittelbar vor dem Stromstoss, unmittelbar nach Schluss des Krampfanfalls, ferner in der Regel 2, 4—5 bzw. 9—10 Minuten nach dem Stromstoss aufgenommen. In mehreren Fällen wurde die Aufnahme unmittelbar nach Schluss des Krampfes durch motorische Phänomene während des Benommenheitsstadiums beim Erwachen erschwert. Ein Hinweis darauf, dass man während des Krampfanfalls keine brauchbaren Kurven erhalten kann, dürfte sich wohl erübrigen.

### *Ergebnisse.*

Die Elektrokardiogramme nach den Valsalvaschen Versuchen sind den nach Elektroschock aufgenommenen Kurven in vielen Beziehungen sehr ähnlich. Der grösste und wichtigste Unterschied liegt in der Schlagfrequenz. Während diese unmittelbar nach dem Valsalvaschen Versuch auf einen Wert sinkt, welcher die Ausgangs-

frequenz oft erheblich unterschreitet, erhält man nach dem Krampfanfall beim Elektroschock meistens eine starke Frequenzsteigerung, was ja auch von älteren Untersuchern angegeben worden war. In dem vorliegenden Material sahen wir Steigerungen von durchschnittlich  $> 30\%$ . Sonst wurden durchweg dieselben Veränderungen im Ekg sowohl nach Elektroschock als auch nach Valsalvaschem Versuch beobachtet. Sie sind im wesentlichen von folgender Art:

1. Höhenzunahme der P-Zacken, namentlich bei  $P_2$ ; bereits im Laufe weniger Minuten, oder noch rascher, Rückkehr zur Norm. Die Veränderung wurde in beiden Serien bei ca  $\frac{3}{4}$  der Fälle festgestellt.

2. Höhenabnahme der R-Zacken, besonders ausgesprochen bei  $R_1$ , in beiden Serien bei  $100\%$ . Der Rückgang erfolgte auch hier in der Regel binnen weniger Minuten; für das Zustandekommen der normalen Höhe der R-Zacken waren jedoch bei einem Teil der Schockfälle mehr als 10 Minuten erforderlich.

3. Veränderung der Höhe der T-Zacken, besonders markant bei  $T_2$ . In ungefähr der Hälfte beider Serien bestanden die Veränderungen in einer Zunahme; bei ca.  $\frac{1}{3}$  wurde keine Veränderung konstatiert, bei dem Rest eine Abnahme. Die Rückkehr zu normalen Verhältnissen nahm gewöhnlich Bruchteile einer Minute, nur ausnahmsweise längere Zeit in Anspruch.

Eine deutliche Senkung des S-T-Abstands wurde nicht beobachtet, was evtl. der vorausgehenden Sauerstoffinhalation zugeschrieben werden kann. Arrhythmien, Reizleitungsstörungen und andere schwerere Veränderungen, welche ältere Untersucher in grossem Umfang gefunden hatten, kamen in diesem Material praktisch überhaupt nicht vor.

In sämtlichen Kurven wurden selbstverständlich alle Zacken gemessen, aber aus Gründen der Platzersparnis werden in den folgenden Tabellen nur die Werte für diejenigen Zacken angegeben, welche die markantesten Veränderungen zeigen ( $P_2$ ,  $R_1$ ,  $T_2$ ). Aus Tab. 1, 2, 3 und 4 wird die Veränderung der Zacken von unmittelbar vor bis unmittelbar nach dem Valsalvaschen Versuch bzw. Elektrokrampf ersichtlich. Daneben findet man die prozentuale Verteilung der Veränderungen.

Tabelle 1.

## Valsalvascher Versuch.

Nr., Geschlecht, Alter d. Ver- suchsperson	$P_2$ in mm un- mittelbar vor d. Versuch	$P_2$ in mm un- mittelbar nach d. Ver- such	$T_2$ in mm un- mittelbar vor d. Versuch	$T_2$ in mm un- mittelbar nach d. Ver- such	$R_1$ in mm un- mittelbar vor d. Versuch	$R_1$ in mm un- mittelbar nach d. Ver- such
1. ♂ 23	3	5	4	8	7	2
2. ♂ 23	3	8	7	8	7	3
3. ♂ 23	2	3	4	4	8	4
4. ♂ 38	1	3	3	4	8	4
5. ♂ 24	3	4	7	5	10	5
6. ♂ 26	2	4	3	4	7	4
7. ♂ 29	2	3	3	3	13	11
8. ♂ 29	1	4	3	3	7	3
9. ♂ 30	3	4	5	3	11	6
10. ♂ 25	1	2	5	5	7	6
11. ♂ 30	2	3	2	4	9	7
12. ♂ 30	3	3	5	6	5	4
13. ♂ 24	2	2	5	5	11	10

Tabelle 2.

## Elektroschock.

Nr., Geschlecht, Alter d. Ver- suchsperson	$P_2$ in mm un- mittelbar vor d. Stoss	$P_2$ in mm un- mittelbar nach Schluss d. Krampfs	$T_2$ in mm un- mittelbar vor d. Stoss	$T_2$ in mm un- mittelbar nach Schluss d. Krampfs	$R_1$ in mm un- mittelbar vor d. Stoss	$R_1$ in mm un- mittelbar nach Schluss d. Krampfs
14. ♀ 17	2	2	3	7	11	7
15. ♀ 23	3	5	2	4	7	5
16. ♀ 57	2	4	2	3	8	5
17. ♀ 51	3	3	3	3	10	9
18. ♀ 32	2	3	3	4	8	5
19. ♂ 35	3	4	5	6	10	9
20. ♀ 54	2	0	2	5	11	7
21. ♀ 46	2	3	2	4	6	5
22. ♀ 21	2	4	5	3	12	9
23. ♀ 32	2	2	2	3	8	5
24. ♀ 44	3	4	1	2	6	5
25. ♂ 56	2	3	4	4	6	4
26. ♀ 51	2	3	3	3	9	5

Tabelle 3.

Valsalvascher Versuch.

P <sub>2</sub>			T <sub>2</sub>			R <sub>1</sub>		
Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle	Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle	Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle
85	0	15	46	16	38	0	100	0

Tabelle 4.

Elektroschock

P <sub>2</sub>			T <sub>2</sub>			R <sub>1</sub>		
Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle	Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle	Zunahme in % d. Fälle	Abnahme in % d. Fälle	Keine Veränderung in % d. Fälle
69	8	23	69	8	23	0	100	0

Aus Tab. 1 und 2 gehen die numerischen Werte in mm für die betreffenden Zacken hervor. Tab. 3 und 4 lehren, dass eine Zunahme von P<sub>2</sub> in beiden Serien ganz dominiert. Eine Abnahme wurde in einem Falle von Elektrokrampf bei einer 54jährigen Person beobachtet. Auch die T-Zacken weisen eine Zunahme erheblich öfter auf als eine Abnahme, obwohl die Zahl der unveränderten Zacken hier grösser ist als bei den P-Zacken. Die Abnahme von R<sub>1</sub> ist der konstanteste Befund im ganzen Material.

Die Beobachtungen stimmen mit älteren Erfahrungen gut überein. Sieht man von den bedrohlichen Komplikationen ab, welche hier völlig fehlen, so ist der Einklang mit den Resultaten von Streit beim Elektroschock ein guter. Auch die Bürgerschen Erfahrungen mit dem Valsalvaschen Versuch lassen sich mit den Befunden der vorliegenden Untersuchung recht wohl vereinbaren. Allerdings liegt ein scheinbarer Widerspruch in der Angabe Bürgers, dass die P-Zacke postpressorisch gänzlich verschwinden kann. Bei Betrachtung des Primärmaterials von Bürger findet man jedoch, dass dies nur ganz ausnahmsweise der Fall war und von



Bürger eher der Seltenheit halber betont wurde. Während der postpressorischen Phase fand auch Bürger durchweg eine Zunahme der P-Zacke.

Aus dem vorliegenden Material lässt sich mithin herauslesen, dass die unmittelbar nach dem Valsalvaschen Versuch und Elektrokrampf festgestellten Veränderungen in vielen wichtigen Punkten auffallend ähnlich sind, was für eine gleichartige Entstehungsweise spricht. Das gemeinsame Moment, welches hierbei in erster Linie in Betracht kommt, ist natürlich die starke Drucksteigerung in der Brust- und Bauchhöhle mit der Rückwirkung, die sie auf den Kreislauf ausübt.

Was die Deutung von Einzelheiten bei den beobachteten Veränderungen betrifft, so steht man grossen Schwierigkeiten gegenüber, begreiflicherweise infolge unserer lückenhaften Kenntnisse in bezug auf die Auslegung der Ekgzacken überhaupt. Eine Höhenzunahme der P-Zacke pflegt man als P pulmonale zu bezeichnen und auf Vorhofhypertrophie oder im allgemeinen auf Drucksteigerung im kleinen Kreislauf zurückzuführen. Letztere Erklärung erscheint hier angebracht, da anzunehmen ist, dass nach sowohl Valsalvaschem Versuch wie Elektrokrampf eine beträchtliche Erhöhung des Drucks vorliegen dürfte. Die Deutung der T-Zacken verursacht erhebliche Schwierigkeiten, weshalb man von einer Erörterung in diesem Zusammenhang nicht viel erwarten kann. Immerhin sieht man nicht selten eine Höhenzunahme der T-Zacken im Arbeitsekg gesunder Individuen. Nordenfelt (1942), der sich speziell mit der Rolle, welche die vegetative Innervation beim Ekg spielt, beschäftigte, hat im Gegensatz zu einigen älteren Untersuchern behauptet, dass das Aussehen der T-Zacken in gewissen Fällen mit dem vegetativen Tonus eng zusammenhängt, u.a. insofern, als Sympathicusreizung eine Verkleinerung derselben bewirkt. Wir müssen uns jedoch bis auf weiteres des Urteils darüber enthalten, ob diese Erfahrungen zur Erklärung hier vorliegender Befunde herangezogen werden sollen.

Wie oben bereits betont wurde, machten sich bei dem vorliegenden Material keine Komplikationen von Bedeutung bemerkbar. Sämtliche im Schrifttum über Ekg beim Elektroschock angegebenen Komplikationen in Form von Arrhythmie, verändertem Reizursprung und Überleitungsstörungen fehlen hier, abgesehen von einer rasch vorübergehenden, sehr geringfügigen Ver-

längerung der Überleitungszeit in einem Fall und einem ebenfalls kurzdauernden nodalen Rhythmus in einem anderen. Die Aufsplitterungen des Kammerkomplexes, welche bei älteren Individuen häufig sind, und den man heutzutage keine entscheidende pathologische Bedeutung beilegt, kommen natürlich auch bei einem Teil unserer älteren Fälle vor. Diese Veränderungen wurden indessen von dem Elektrokrampf nicht ungünstig beeinflusst, in einem Fall verschwand sogar eine derartige »Anomalie« nach dem Krampf für wenige Minuten.

Da die einzelnen Kurven über die in den tabellarischen Zusammenstellungen angegebenen Einzelheiten hinaus keine Aufschlüsse von wesentlichem Wert vermitteln, wird auf eine Wiedergabe derselben an dieser Stelle verzichtet. Als typische Beispiele seien nur zwei Kurvenabschnitte bei einem Fall von Elektrokrampf



Abb. 1. Ekg unmittelbar vor Elektroschock.

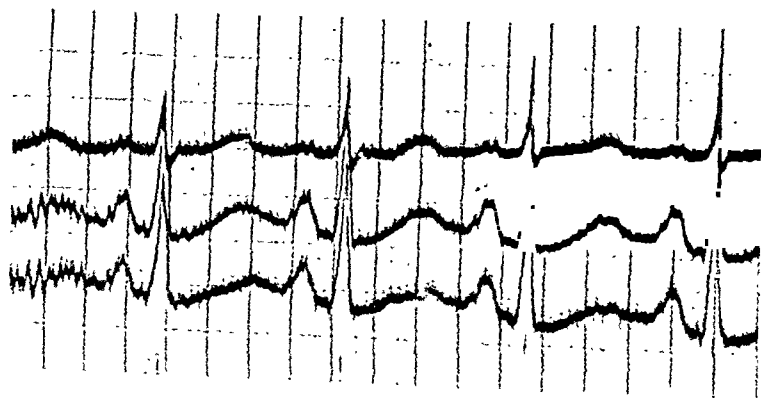


Abb. 2. Ekg unmittelbar nach Beendigung des Krampfanfalls.

unmittelbar vor dem Stromstoss bzw. unmittelbar nach Schluss des Krampfs angeführt.

Das Ekgmaterial und die übrigen Erfahrungen bei der Elektroschockbehandlung scheinen uns eine optimistischere Beurteilung des Einflusses dieser Therapie auf das Herz zu rechtfertigen, als es nach einer Reihe von älteren Arbeiten im Schrifttum den Anschein hat. Das Ausbleiben bedeutsamer Komplikationen kann freilich auf die Zusammensetzung des Materials zuzückzuführen sein, aber die günstigen Ergebnisse stimmen, wie oben angegeben wurde, durchaus mit den in der Psychiatrischen Klinik gemachten allgemeinen Erfahrungen überein, laut welcher der Elektroschock nicht einen für das Herz allzu bedrohlichen Eingriff darstellt.

### Zusammenfassung.

Von früheren Erfahrungen ausgehend wird die Möglichkeit erörtert, dass die Kreislaufstörungen beim Elektroschock eine gleichartige Genese haben können wie die beim Valsalvaschen Versuch beobachteten. Elektrokardiogramme zweier Serien von je 13 Fällen mit Elektrokrampf und Valsalvaschem Versuch werden miteinander verglichen und weisen grosse Übereinstimmungen auf. In beiden Fällen findet man bei der Mehrzahl der Kurven eine Höhenzunahme der P- und Höhenabnahme der R-Zacken. Die T-Zacken verhalten sich mehr wechselnd, lassen aber nichtsdestoweniger in der Mehrzahl der Fälle in beiden Serien eine grössere Höhe erkennen. Da zuvor nachgewiesen worden ist, dass beim Elektrokrampf eine hochgradige Drucksteigerung in der Brust- und Bauchhöhle zustande kommt, macht es den Anschein, als ob die Ekgveränderungen beim Elektroschock im wesentlichen gleichen Ursprungs und Wesens wären wie diejenigen, welche nach dem Valsalvaschen Versuch auftreten.

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## On the Frequency of Séropositive Syphilis in Norway in Presumably Healthy Adults.

By

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Besides the annual official reports on new cases of syphilis, the frequency of this disease in the Norwegian population has hitherto chiefly been illustrated by examinations on autopsy material, and investigations in hospital departments.

In the postmortem examinations from Gades Institut in Bergen during the period 1909—1940, Magne Svendsen (29) finds syphilis in 416 of 6036 postmortems, or in  $6.89 \pm 0.9$  per cent. Among 3290 men, syphilis was found in 292 or 8.9 per cent, and among 2746 women in 124 or 4.5 per cent. The previous similar Norwegian investigations in this field are also quoted here.

Chr. Giertsen (12) examined a material consisting of 4004 men, 4238 women, and 625 children treated in the internal department of Haukeland Hospital, Bergen, in the interval from 1925 to 1932. He got positive information of syphilis infection anamnestic, clinical or serological in 418 or 10.44 per cent of the men, and 144 or 3.40 per cent of the women; further 23 cases of congenital syphilis not counted in the material. 290 among the 562 patients with syphilis were hospitalized on account of diseases connected with syphilis, but in 275 cases the demonstration of syphilis was merely accidental; that makes 3.3 per cent of the patients, 5 per cent of the men and 1.8 per cent of the women.

Haakon Sæthre & Alf Bretteville-Jensen (30) found in a mental department syphilis in 269 of 1525 patients, or in 17.63 per cent; 25.2 per cent in men and 9.7 per cent in women.

Th. M. Vogelsang (34) examined in the material from Gades Institut, Bergen, 15,097 serums from patients hospitalized for diseases not connected with syphilis and from some presumably healthy persons. Among these, 3.8 per cent had more or less positive syphilis reactions.

T. Holst-Larsen (17) investigated a material from Ullevål Hospital VII. Div., Oslo, (internal department), for the years 1939 and 1940. Among 3687 patients, 1730 men and 1957 women, he finds a syphilis frequency of 5.6 per cent, 7.7 per cent in men and 3.9 per cent in women. The percentage of latent syphilis within different age groups of the total material is also stated.

The present authors (16) recently demonstrated seropositive syphilis in 8 of 1136 cases, or  $0.7 \pm 0.25$  per cent, among persons volunteering as blood donors in the Norwegian Red Cross' Blood Donor Service in Oslo.

In Sweden and Denmark several investigations have been carried out on the frequency of syphilis in hospital departments. Much of this material has been very carefully evaluated and subdivided in different groups, in sex, and in a few also in age groups. The table 1 only contains the chief figures of these examinations.

The material originates from different hospital departments; the investigations of Borberg & Petersen from an insane asylum; Boesen, and Lindahl from surgical departments; and Kallner from a medical outdoor department. The remaining material is derived from medical departments.

By the nature of the case it is not possible to use these investigations for the estimations of the syphilis frequency in the population. There is reason for supposing that a relatively high frequency is to be found in medical departments, and a somewhat lower frequency in surgical ones. Kallner, however, has distinguished patients applying to a medical out-patient department with symptoms not connected with syphilis. He states that among 54 cases of accidentally recognised syphilis 42 had a negative anamnesis, and in 28 cases or about the half of the total neither anamnesis nor clinical examination were able to reveal the infection.

Table 1.

*Investigations on Syphilis Frequency in Sweden and Denmark.*

Authors	Period of investigation	Number investigated	Syphilis percentage
<i>Denmark</i>			
Scheel (26) and Faber (10) . . . . .	1914—1915	1,356	9.1
Jørgensen (18) . . . . .	1923—1929	5,158	8.8
Reymann & Wendelboe-Jørgensen (24) . . . . .	1937	1,522	5.7
Borberg & Petersen (5) . . . . .	1939	1,035	5.5
Soby & Nielsen (31) . . . . .	1935—1940	14,140	2.4
Aggerbeck (1) . . . . .	1936—1940	13,822	2.1
Boesen (4) . . . . .	1935—1942	8,539	0.7
<i>Sweden</i>			
Eldh (9) . . . . .	1925—1931	17,108	2.2
Forssman (11) (also published by Ingvar) . . . . .	1928—1931	7,711	2.5
Kallner (19) . . . . .	1938	7,550	0.7
Lindahl (20) . . . . .	1939—1940	5,494	0.8

Reymann (22) has estimated the syphilis frequency in the Danish merchant marine. Among 837 officers and men he finds 99 persons with syphilis, or 11.8 per cent. The frequency varies between the different groups of merchant mariners. In another investigation (23) he finds that among 627 persons with fresh syphilis infections 269 or 42.9 per cent were infected abroad, and that seamen were responsible for 94 per cent of the syphilis importation.

Seamen in their native country are not more frequently infected with syphilis than their countrymen, but owing to their occupation they spend part of their life overseas, in a milieu often heavily infected with syphilis, as in many seaport towns; they are conclusively exposed to a greater risk of infection. Between other respectable orders of society one may not expect great differences in the syphilis frequency in this country, as matters stand. Even among 1200 women compulsorily examined through the municipal health department of Oslo, Borgen (6) found only 85 seropositive or 7.1 per cent. Most of these investigated were women with a rather lax morality, either charged as sources of infection with venereal diseases, or seized for compulsorily examination in police raids on certain coffee-houses.

In Finland 527 Carelian factory workers were examined by Majjala (21). He found the Bordet-Wassermann reaction positive in 8 cases, the Kahn test in 11, and the Müller Ballung test in 14 cases. Only 3 of the workers were aware of their infection; they had previously been treated and thought themselves cured.

The latter investigation is confined to a single district and a certain occupation and includes comparatively few persons, so that it is not possible to form an idea of the syphilis frequency within the different ages; and even if it is based upon presumptively healthy persons the investigation can therefore not be considered representative of the Finnish population.

The investigation of Reymann deals with a selected material with a high exposure to infection. The material of blood donors recently examined by the present authors is also a selected material, as it only includes persons not aware of any syphilitic infection; persons knowing of their syphilitic infection do not volunteer as blood donors.

In the Scandinavian countries therefore up to the present time no investigation has ever been made on the frequency of syphilis in presumptively healthy persons, in a material considered to be representative of greater parts of the population of the country.

### Personal investigations.

#### *Material.*

Our material consist of blood samples from 10,453 presumably healthy persons, some of them policemen, but for the greater part belonging to the Civil Air Defence. The determination of the blood groups is obligatory in these services, and was carried out during the years 1940 and 1941 in the State Institute for Public Health, Wassermann division. The blood samples were collected by different physicians and forwarded to the laboratory.

The aim of the blood grouping is that every man in the services concerned should know his own blood group in the case of injuries to himself caused by air raids requiring treatment with blood transfusion, but also in order to enable him to give blood to injured fellow comrades. To minimize the danger of syphilis transmission, all blood samples were examined with serologic syphilis tests, because we, from our experience in the Norwegian Red



Cross' Blood Transfusion Service in Oslo considered this to be a necessary precautionary measure (16). In the case of positive reactions, a new blood sample was taken later by the physician as a control. The interval between the first and second blood sample varied from 14 days to more than a year. At the same time the physician was requested to procure clinical and anamnestic information from the man.

The Civil Air Defence men consist of people from the most different occupations and orders of society, previously organised in the Red Cross' Auxiliary Corps, the Workmens Sanitary Service and similar associations; and different craftsmen and skilled workers; and also tradespeople and others who lost their incomes in the beginning of the German invasion of Norway and got a temporary paid job here. The firemen have also been included in the Civil Air Defence Corps. Civil Air Defence services are established in all towns and industrial centres of any significance throughout the country. Our investigations involve the southern parts of Norway including Trøndelag. The number of men employed in the Civil Air Defence Corps is roughly proportional to the fixed population in every place. We have not been able to demonstrate any differences in the rate of positive reactions between policemen and Civil Air Defence men, nor could we statistically prove any distinct variations between the different towns, nor between single towns nor between groups of them as seaside and inland towns. In the further discussion of the investigations we will therefore consider the material as a whole.

In investigations of this kind one might imagine that patients who knew that they suffered from syphilis would refuse the collection of a blood sample in order to keep this fact secret. And as a matter of fact, one of the men showing positive reactions told us that if the blood grouping tests had not been obligatory, he would not have delivered any blood sample, just in order to avoid the detection of his syphilitic infection. And even though the blood examinations were obligatory, we were far from having got blood samples from all men in the services. But refusal was principally caused by the people's fear of being used as blood donors for the benefit of the enemy and against their will. This was caused by rumours naturally arising among the people during war and enemy occupation and doing their work in different places, whereas in

most localities few or none refused the blood grouping tests. The latter localities did not show any higher percentages of seropositive syphilis than the former ones. And as a rule, the men did not imagine that the blood samples were examined with syphilis tests, but thought that it was only the blood group which was determined. We therefore assume that the men knowing of their syphilitic infection and for that reason having refused the blood grouping, must have been very few and consequently do not noticeably influence the value of our investigations.

From the foregoing it will be seen that our material must be considered representative of the towns and densely populated industrial centres in Southern Norway.

In all cases we have obtained information about sex and age, thus enabling the subdivision of the material in men and women, and in age groups. This is certainly of paramount importance in every study of syphilis distribution, but has only been paid sufficient attention to by a few investigators in this field. As an example of the conspicuous differences of syphilis frequencies with age, we can mention the investigations of Blount (3) on 5,000 American soldiers. He found among recruits a syphilis percentage of 0.52 in men between 18 and 23 years, and 5.5 in those between 30 and 35 years. In soldiers with previous service he found 1 per cent syphilis in the age group 20 to 23 years, and 18.1 per cent for men between 42 and 59 years.

### *Methods.*

The syphilis tests were carried out in direct connection with the blood grouping tests, according to the method previously described by one of us (14). As a routine we use in this laboratory simultaneously the Bordet-Wassermann reaction, Mcinicke's clarification test II. and the Wadsworth & Brown reaction in all serums. The latter is a very efficient modification and improvement of the Kahn test, introduced in this country by Th. Thjøtta (7). It would be rather impracticable, however, to use our routine method for the present mass investigation where the great majority of the serums certainly would be negative on all reactions, and we had therefore to adapt a method most efficiently and readily able to strain off the positive serums; and then afterwards reinvestigate the latter throughout by aid of the routine method, and additional

reactions. In doing so, we could save a considerable amount of unnecessary labour.

The syphilis test most commonly used for mass examinations is Meinicke's reaction. Sæthre & Bretteville-Jensen (30) have in our country recommended that the clinician himself perform the Meinicke reaction in the serum from the patient, and only forward the positive tests for a closer examination in a serological laboratory. We agree with these authors in that Meinicke's reaction is excellent for mass examinations, and perhaps also the most sensitive precipitation test among all those having the necessary specificity. Still we had the impression that we in our routine material not infrequently had serums from syphilitics showing positive Bordet-Wassermann, but negative Meinicke's reactions. Vogelsang (33) also warns against the use of Meinicke's test as the sole reaction.

By examining our routine material for the recent period we found among 36,356 samples (the present investigation not counted) 5,415 showing distinct positive Bordet-Wassermann reactions; including 203 samples exhibiting negative Meinicke's reactions. They are divisible in the following way:

*Positive Serums with Negative Meinicke's Reaction.*

	Syphilis	Dubious	Non-specific	Sum
Bordet-Wassermann + Wadsworth-Brown + Meinicke — . . . . .	87	13	17	117
Bordet-Wassermann + Wadsworth-Brown — Meinicke — . . . . .	51	8	27	86
	138	21	44	203

As we do not always receive diagnosis and clinical information about the blood samples forwarded to the laboratory, it is indeed possible that some of the 21 reactions above characterised as dubious actually are caused by syphilis. The 44 reactions described as nonspecific have been diagnosed as not caused by syphilis by repeated tests and in other ways, so that we in all these 44 cases with certainty can exclude syphilis as the cause of the positive reaction.

If we for the sake of caution only reckon the 138 reactions connected with positive information about syphilis, we get the same the result that Meinicke's reaction fails in  $2.5 \pm 0.2$  per

cent of the positive reactions. It may also be termed as follows: Persons with syphilis with positive Bordet-Wassermann's reactions have in 2 to 3 per cent negative Meinicke's reactions.

We therefore supposed that the best method for straining off the positive serums would be the simultaneously application of the Bordet-Wassermann reaction and Meinicke's reaction. Meinicke's reaction was only set up in the main series. In this way one would miss the positive reactions of prepotent strength, as these do not show any clarification in the main series; but they are very infrequent, and in our routine material we never saw serums giving Meinicke's reaction of this kind and simultaneously negative Bordet-Wassermann reactions. The Bordet-Wassermann reaction was set up in a single dose of  $0.2\text{ cm}^3$  serum, without any serum control tube. Our method was therefore very simple, requiring only two test tubes, one for the Meinicke and one for the Bordet-Wassermann reaction.

The method employed was consequently the following: Simultaneously with the pipetting of serum for the agglutinin determination in the blood grouping tests,  $0.2\text{ cm}^3$  serum for the Meinicke reaction and  $0.2\text{ cm}^3$  serum for the Bordet-Wassermann reaction were also pipetted off in their respective tubes. When all samples have been manipulated, the rack of tubes containing the serums for the Bordet-Wassermann reaction was incubated in a water bath at  $55\text{ C}$  for fifteen minutes. Thereafter to every tube was added  $0.3\text{ cm}^3$  physiological saline solution,  $0.5\text{ cm}^3$  Wassermann antigen suspension, and  $0.5\text{ cm}^3$  complement solution in the ordinary way, the rack incubated in a water bath at  $37\text{ C}$  for half an hour and the sensitised sheep cells added. The rack was replaced in the water bath for ten minutes and the results then read. All samples showing the slightest trace of positive reactions in one or both tests were afterwards thoroughly reexamined by our routine method with a complete Meinicke's reaction, the Wadsworth & Brown reaction, and the Bordet-Wassermann reaction with the serum doses of  $0.2$ ,  $0.1$ ,  $0.05$ , and  $0.025\text{ cm}^3$ , and a serum control tube containing  $0.2\text{ cm}^3$  serum; as well as additional syphilis tests.

For the Meinicke reaction we regularly employed the antigen produced by Astra (Sweden), which has yielded constant and good results in the period we have used it, and which one of us has previously shown and laid down in a special communication (13). For

the Wadsworth & Brown reaction we have produced the antigen ourselves after the method specified by the inventors, and used the original procedure for the reaction, and not the modification proposed by Borgen & Natvig (7). This reaction has in our hands shown approximatively the same sensitiveness and specificity as the Meinicke reaction.

The positive serums were preserved in a frozen state in a refrigerator for later supplementary examinations.

Besides the reactions employed for the routine tests we have also used a number of collateral reactions by way of making sure whether the positive reactions were nonspecific or were caused by syphilis. These reactions were the Palligen reaction, the Kahn standard reaction, the Müller Ballung (conglobation) reaction, the Sachs & Georgi reaction (lentocholesterol reaction), and the Sachs & Witelsky reaction (citochol reaction).

In order to detect nonspecific reactions, the Palligen reaction is of superior importance. This reaction has been carried out with an antigen produced by Sächsische Serumwerke, Darmstadt, Germany. The antigen consists of a suspension of a culture of *Treponema pallidum*, to be used with an addition of equal parts of a 0.3 per cent phenol solution for a complement fixation reaction. Whereas the Bordet-Wassermann reaction is caused by heterophile antibodies, the Palligen reaction is considered a specific reaction, and this is supported by experiments carried out by different investigators. The Palligen reaction was first employed in this country by Vogelsang (34), who has published his experiences with this test in several communications.

It is now currently known that syphilitic serums giving a positive Bordet-Wassermann reaction, after an appropriate absorption with the Wassermann antigen still give a positive Palligen reaction, whereas the Bordet-Wassermann reaction after the absorption turns negative. The Palligen reaction has thus efficiently been instrumental in our investigations to decide whether the positive Bordet-Wassermann reactions were specific or nonspecific. We have encountered some cases giving a very strong positive Bordet-Wassermann reaction, also confirmed by examinations in two additional serological laboratories, but showing a completely negative Palligen reaction also without preceding absorption with the Wassermann antigen. Reactions of this type, which are

not also supported by positive precipitation tests, certainly are nonspecific. We have detailed elsewhere (15) two cases of these nonspecific reactions relating to father and son.

The Palligen reaction was carried out according to the specifications in the directions from the manufacturers and also employed by Vogelsang, but with the addition of a titration of the serum by the use of more serum doses, as in the Bordet-Wassermann reactions. In so doing we got the impression that the Palligen reaction commonly gave the same titer as the Bordet-Wassermann reaction. Still we hold the opinion that the Palligen reaction, using a rather anticomplimentary antigen, can in no way enter into competition with the Bordet-Wassermann reaction as a routine method; but it is a superior test to decide if a positive Bordet-Wassermann reaction is specific or nonspecific, in doubtful cases.

For the Kahn, Müller, lentochol and citochol reactions we have used commercial antigens, and followed the accompanying directions for use.

Among the 161 persons showing positive reactions on one or more tests, we obtained additional blood samples from 110. From a few persons we got even more blood samples, in cases of nonspecific reactions, in order to subject them to a closer study. From 18 of the others we thought it unnecessary to collect new samples, as they during the intervening time admitted the knowledge of their syphilitic infection. A total of 33 persons refused the collection of a new blood sample for syphilis tests. Some of these too certainly have refused because they knew that they previously had a syphilitic infection. In these cases we are forced to support our decision of the diagnosis on the examination of a single blood sample, however with several sensitive and specific reactions. Of these 33 cases we have considered 23 as caused by syphilis, and 10 as dubious or nonspecific reactions.

Clinical and anamnestical information was procured in 100 cases.

### *Results.*

Among the 10,453 persons examined, 161 showing positive syphilis reactions in one or more blood samples were found. By a closer examination with the aforementioned supplementary reactions, as well as with the aid of the collected clinical and anam-

nestical information, we estimated that 122 of the cases with certainty or predominant probability were caused by syphilis, while 21 certainly were nonspecific, and 18 dubious.

Of the 122 specific reactions 96 were positive in all tests, whereas 26 were positive only in the precipitation tests. Of these 26, 10 admitted their syphilitic infection, 7 claimed ignorance of their infection, and 9 gave no information at all.

The nonspecific reaction as a rule were of a transient nature. Some of them were isolated transitory positive Bordet-Wassermann reactions, of which we have described elsewhere two of the cases with a familiar occurrence (15). Others were positive both in the Bordet-Wassermann reaction as well as in some of the precipitation tests, but negative in the Palligen reaction and transitory. In one case the Bordet-Wassermann reaction has been very strongly positive during the whole period of our observation and remains still strongly positive, while the Palligen reaction and all precipitation tests remain completely negative. The positive Bordet-Wassermann reaction in this case has also been confirmed by examination in two other serologic laboratories. Most of the nonspecific reactions have been positive Meinicke's reactions chiefly of a transitory nature, but also some remaining positive in repeated samples. The latter originated from some allergic persons, where we have the impression that isolated constantly positive Meinicke's reactions of a nonspecific character are not infrequently met with.

18 of the positive reactions we have characterised as dubious, and not counted them in our material of positive reactions. Most probably, however, some of them have been due to syphilis, but the bulk of them have been feeble reactions only positive in some of the precipitation tests, and they could therefore as a rule not be counted as representing distinct seropositive persons, even if we possessed anamnestic information about syphilis infection.

Vogelsang (34) in his material from Gades Institut in Bergen had a considerable number of positive reactions in patients suffering from malaria, which reactions he thought to be nonspecific. Most of the persons in our material have been questioned as to malaria infection, and 87 of them state that they previously have been infected with malaria. Of these, 83 were completely negative on all syphilis tests, and 4 had positive reactions. Of the four,

one had suffered from a primary syphilis and had been treated with one course of injections in a Scandinavian hospital, but the three others were unaware of any syphilitic infection. But as all reactions were distinctly positive in these three persons, we have counted them among the reactions with certainty or predominant probability caused by syphilis. We hold the opinion that if the Bordet-Wassermann reaction is more frequently positive in persons previously suffering from malaria than in other persons, it may naturally been explained by the fact that the former, in the milieu where they contracted malaria fever, also had a greater chance than others to be infected with syphilis. In an investigation from Sweden, Gunhild Bergstrom (2) also claims that malaria patients not often show nonspecific positive syphilis tests, while in the literature the frequency of nonspecific Bordet-Wassermann reactions in malaria patients is stated with very different percentages, from 0 to 80. Our material includes strictly speaking not malaria patients, but only persons who on some occasion or other have gone through a malaria fever, but for the present are free from symptoms.

In an investigation of this kind one must not too readily count transitory positive reactions as nonspecific. In one of the cases showing a weakly positive Bordet-Wassermann reaction and strongly positive precipitation tests, a new sample collected 14 days later exhibited completely negative reactions in all tests. We would have been forced to count the positive reactions in the first sample as nonspecific, if our register had not informed us that the identical man a year previously had been under treatment for syphilis, and that a blood sample taken on that occasion had been completely positive. The man had accordingly been treated in the interval between the taking of the two last samples, and was on the last occasion in a seronegative phase. In another case the first sample showed a feebly positive Bordet-Wassermann reaction and precipitation reactions of medium strength, whereas the supplementary sample taken 3 months later was completely negative in all tests. This patient then informed us that he was under treatment for syphilis.

9 persons giving only positive reactions in some of the precipitation tests admitted a previous syphilitic infection. If we in these cases had not possessed the anamnestic data, we would have counted the reactions as dubious.



The persons examined included 9,531 men and 922 women. Among the men 115 had positive syphilis reactions, and among the women 7. For men we therefore find in the collected material a frequency of seropositive syphilis of  $1.2 \pm 0.1$  per cent. Such a figure, however, does not tell us much; a considerably greater importance must be attributed to the distribution of the cases within the different ages, which is shown in table 2.

Table 2.

*Age Distribution of Seropositive Syphilis Cases in 9531 Norwegian Men.*

Age years	Number of persons examined	Cases of seropositive syphilis	Age years	Number of persons examined	Cases of seropositive syphilis
15	16		48	243	5
16	42		49	198	5
17	108		50	216	5
18	184		51	165	1
19	219	1	52	177	3
20	260	2	53	161	4
21	216	1	54	122	5
22	301	1	55	136	2
23	267		56	110	2
24	269	1	57	103	2
25	282		58	98	2
26	269	2	59	80	
27	261		60	66	2
28	280	3	61	62	3
29	273	1	62	46	1
30	277	1	63	46	2
31	240	2	64	44	2
32	266	2	65	27	1
33	229	1	66	30	2
34	264	4	67	8	
35	240	1	68	11	1
36	216	3	69	4	
37	201	6	70	5	
38	222	3	71	3	1
39	221	3	72		
40	207	4	73	1	
41	197	5	74	1	
42	217	3	75	1	
43	239	2	76		
44	198	3	77		
45	203	3	78	1	
46	221	4	79		
47	260	2	80	1	
Sum 9531					115

It will be seen that the number of seropositive men increases with age. This appears more distinctly if the material is arranged according to age groups and the percentages calculated in every group, as shown in table 3.

Table 3.

*Frequency of Seropositive Syphilis in Different Age Groups in 9531 Norwegian Men.*

Age group	Number of men examined	Number of seropositive men	Percentages seropositive men	Dubious reactions	Nonspecific reactions
15-19.....	569	1	$0.18 \pm 0.18$	1	1
20-29.....	2678	11	$0.41 \pm 0.12$	3	7
30-39.....	2376	26	$1.09 \pm 0.21$	4	3
40-49.....	2183	36	$1.65 \pm 0.27$	7	2
50-59.....	1368	26	$1.90 \pm 0.37$	1	3
60 and more ....	357	15	$4.20 \pm 1.06$	2	2
	9531	115		18	18

The table indicates a distinct uniform augmentation of the syphilis frequency with increasing years. However, the standard error of the differences between the percentages from neighbouring groups show that the differences in most cases are not statistically significant. To get a more decisive proof that the frequency of syphilis increases with age in this material, we must compare larger age groups, and as most suitable we can choose the age groups from 20 to 39, and from 40 to 59 years. The figures will then be:

Age group	Number of men examined	Number of seropositive men	Percentages seropositive men
20-39	5054	37	$0.73 \pm 0.12$
40-59	3551	62	$1.75 \pm 0.22$

The standard error of the difference is here  $\sqrt{0.12^2 + 0.22^2} = 0.25$ . As the difference is  $1.75 - 0.73 = 1.02$ , it is more than four times the standard error, i. e. the odds are more than one to 17,000 that the difference is not only a matter of chance.

There are three main factors which cause the augmentation of syphilis frequency with increasing age:

1. The higher ages have been exposed to the risk of infection during a longer period than the younger ones.

2. The number of new syphilis cases has been decreasing during the last decades of years, resulting in a lesser risk of infection for the younger ages; chiefly as a consequence of a better treatment of sources of infection.

3. Comparatively more persons of younger ages have received early and intensive treatment and are thus rendered seronegative.

We obtained clinical and anamnestic information about 83 of the 115 seropositive men. 44 of them stated that they had no knowledge of their infection, whereas 39 admitted the knowledge of having been infected with syphilis. Of these 39 men, 14 were infected in Norway and 7 overseas, but 18 did not mention the place of infection. 33 men were able to specify the year when the infection had taken place, as shown in table 4.

Table 4.

*Date of Syphilis Infection among 33 Seropositive Men.*

Year	Cases	Year	Cases	Year	Cases
1902	1	1920	2	1932	2
1907	1	1923	1	1935	1
1909	1	1924	2	1937	1
1914	1	1925	3	1938	2
1917	3	1926	2	1939	2
1918	1	1928	1	1940	2
1919	1	1931	1	1942	2

It appears that about the same number have been infected in each of the three last decennia, but only 3 before 1910. The age when infected varied between 18 and 47 years, averaging 27 years.

11 men stated that they had been sailors for a shorter or longer period; of these 8 knew of their infection and 3 did not.

Of the 39 men knowing of their infection with syphilis, 11 stated nothing about the treatment, whereas 2 admitted that they had not had any treatment at all. 26 stated that they had been treated, and 24 of these informed us about the kind of treatment. This is summed up in table 5.

Table 5.

*The Kind of Treatment in 24 Seropositive Men.*

Number of men	Kind of treatment	Number of men	Kind of treatment
1	one course of arsenic injections	1	1 course of injections
1	1 injection	1	2 courses of injections
1	2 injections	1	17 injections
1	3—4 "	1	22 "
1	some "	1	24 "
1	5 "	1	30 "
1	6 "	2	32 "
1	7 "	4	more courses of combined injections
1	8 injections of bismuth	1	60 injections
2	10 injections		

The term injection signifies one injection of salvarsan or salvarsan derivatives, singly or combined with bismuth injections.

It will be seen that most of the men have undergone insufficient treatment. A very few of them, however, were under treatment at the time of this investigation.

As a rule it was not possible to distinguish between congenital and acquired syphilis in our material. In 3 cases, however, we could ascertain the occurrence of congenital syphilis by examining the family. The single case among the 569 investigated within the age group 15 to 19 years thus turned out to be congenital, and among the eleven seropositive cases between the 2678 investigated men within the age group 20 to 29 years 2 were congenital, 2 acquired, whereas 7 did not know of their infection. It is highly probable that also some of the latter have been congenital infections.

Of 84 seropositive men, 83 did not show any certain sign of syphilis by ordinary clinical examination, and one had symptoms of tabes dorsalis. We are convinced, however, that closer investigations would expose pathological changes in many more of them.

The occupations of the 115 seropositive men were as follows:

28 skilled workers	9 unskilled workers
20 craftsmen	8 subordinate officials
16 policemen	8 business men
11 firemen	4 occupation not stated
10 chauffeurs	1 student

In addition to the 9,531 men, 922 women have also been examined, of whom 7 were found to be seropositive. Of these 5 did not know of their syphilitic infection, one was under treatment for syphilis, and one gave no information. The seropositive women had the age distribution as shown in table 6.

Table 6.

*Distribution of Syphilis Frequency in 922 Norwegian Women.*

Age group	Number investigated	Number seropositive	Percentages seropositive
15—29.....	528	1	0.2 $\pm$ 0.2
30 and above.....	394	6	1.5 $\pm$ 0.6
All women	922	7	0.8 $\pm$ 0.3

The difference of the percentages within the two age groups is somewhat more than twice the standard error of the difference, giving odds about 25 to one that the difference is a real one and not only caused by chance.

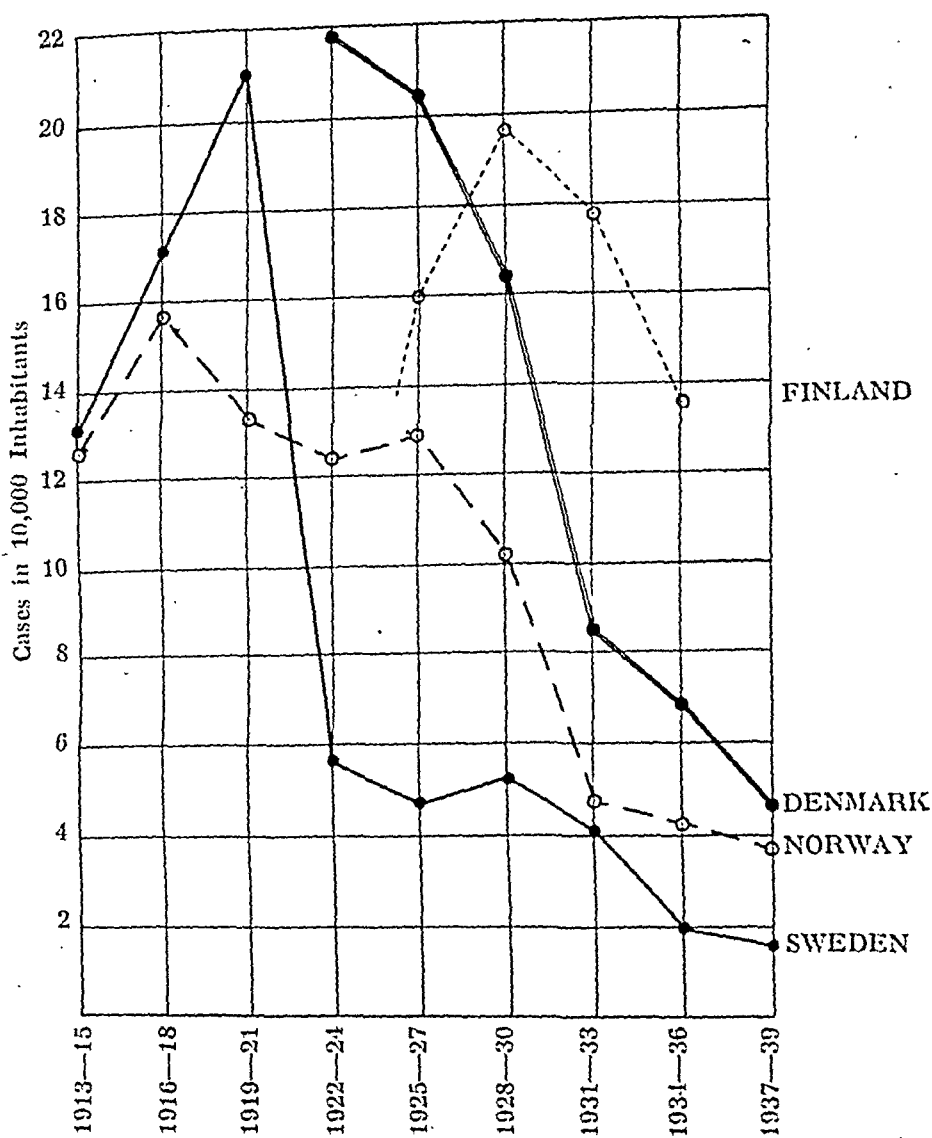
Of the seven seropositive women, 3 were telephone operators (the occupation of a great part of the investigated material of women), one skilled worker, one housewife, and one with occupation not stated.

### *Discussion.*

The graph shows the number of new syphilis cases per 10,000 inhabitants in periods of three years in Denmark, Finland, Norway, and Sweden. The figures for Denmark include also congenital syphilis, so the cases of acquired syphilis for that country will be somewhat fewer than appear in the graph.

It will be seen that the number of new syphilis cases in Denmark, Norway, and Sweden has been rapidly decreasing. The American Albert E. Russel (25) comments on this: »the Scandinavian countries have given the world an excellent example of the effect of concerted effort to eradicate the menace of venereal diseases.» After the German invasion, however, the situation in Norway has been changed; following a minimum of new cases in 1940 the number of infections is again rapidly increasing, especially in women. The conquest of this disease therefore will still be a problem for us for a long time to come.

*The Decrease of New Syphilis Cases in the Scandinavian Countries  
1913—1939.*



A great number of syphilis cases will not appear in the official statistics. Of the seropositive persons in our material giving information, 40 admitted the knowledge of their syphilitic infection, whereas 49 claimed ignorance of their infection. Even if we may not trust too much to the information received from the patients about the disease in question, we suppose it can be taken for granted that the majority of the 49 were untreated or insufficiently treated cases. Assuming the justification of drawing conclusions from our mate-

rial, there should exist in Norway more than 10,000 syphilis patients all unsuspecting of their infection, or about one in 200 persons.

Such cases of syphilis can not be traced in any other efficient way than by serologic examinations. The American Social Hygiene Society reports experience in this field as follows: »in the course of physical examinations when blood tests were made only when syphilis was suspected, 0.6 (six-tenths, or less than one) case was found per thousand compared with forty-four in 1,000 when routine blood tests were made. The ratio is about 1 to 73. This emphasizes the difficulty encountered in attempting the diagnosis of syphilis by physical examination alone» (25).

These untreated cases of syphilis represent a serious medical problem. Even if the investigations of Bruusgaard (8) seemingly prove a great tendency of spontaneous cure in syphilis, most of the recent investigators agree that the serious complications chiefly occur in untreated, tardily treated, or insufficiently treated cases. Thus Strandberg (28) states that out of 461 cases of syphilis in the central nervous system only 4.12 per cent have undergone vigorous treatment from the beginning of the infection. Of tabes, tabo-paralysis, and dementia paralytica, only 1.63 per cent have been well treated from the beginning. And in the same clinic, M. Tottie (32) observed that only 1.4 per cent of vascular syphilis cases were thoroughly treated from the very onset of the disease, while only 2.8 per cent received any salvarsan treatment. 68.1 per cent were not treated at all, whereas 27.7 per cent from the very beginning were treated only with mercury or bismuth.

The prevention of these consequences of syphilis can only be achieved by sufficient treatment and observation of all syphilis cases. We therefore hold the opinion that greater efforts must be devoted to the problem of tracing the cases of unrecognised syphilis in the future. Many cases will be detected if all patients in hospitals are subjected to routine serologic syphilis tests. In hospitals lacking serologic service a routine test with Meinicke's reaction performed with a suitable antigen (13) is better than nothing, as this test will detect 97 to 98 per cent of all seropositive cases. The most important of such examinations will be in medical departments and maternity hospitals. The use of routine serologic tests for syphilis in hospitals is increasingly accepted in our country.

Further, premarital serologic syphilis tests ought to be established

by law, as already done in many other countries. In this way, most of the adult population gradually will be controlled in a period of life where the syphilis diagnosis is of special importance. During premarital examinations in West Virginia, Sheppe (27) found among 677,832 persons 1.3 per cent seropositive, of whom a large percentage did not know of their infection.

If social medicine in our country will be able to continue its previous rapid growth after the intermission caused by war and occupation, more groups of society may be examined with routine syphilis tests, primarily all industrial workers. Such investigations will yield a good return in the saving of lost working power and expenses for hospital and medical treatment, not to mention what may be saved in needless human suffering in the future.

The importation of syphilis by seamen will presumably continue its decrease owing to the better organisation and more ready access to medical advice arranged for the benefit of Norwegian seamen before the last war; but close attention must still be paid to this problem in order to develop additional precautionary measures.

The mere tracing of syphilis cases, however, is insufficient and only half-done work. It is equally necessary to take care that sufficient treatment is carried out and the necessary controls effectuated. It is plain to everyone that it is a great risk to leave this to the initiative of the individual patient. Thus in the present material many of the patients previously not aware of their infection are now regularly treated, but on the other hand, the greatest part and among them many beforehand knowing of their syphilitic infection refuse any treatment at all. We therefore hold the opinion that the enacted obligation of all syphilis patients to subject themselves to the necessary medical treatment and control is inevitable, if an attempted prevention of syphilis complications shall lead to good results, to the benefit of the individual patient as well as to the community.

### Summary.

The frequency of seropositive syphilis in Norway among presumably healthy adults: A total of 10,453 persons, 9,531 men and 922 women, have been examined. The examined persons are considered representative of towns and residential districts in Southern Norway. After minute investigations there were found



1.2  $\pm$  0.1 per cent seropositive syphilis among men and 0.8  $\pm$  0.3 per cent among women. The distribution on age groups will appear from table 3 and table 6, respectively. More than the half stated that they were not aware of their disease. On ordinary examination, clinical symptoms of the disease were ascertainable only in a very few cases. Most of those who were aware of their disease had received insufficient treatment (table 5). The importance of tracing as many as possible of these cases of ignored syphilis and of subjecting them to treatment is emphasized, and directions are given in that respect.

### Résumé.

La fréquence de syphilis séropositive en Norvège chez des adultes présomptivement bien portants: En tout on a examiné 10,453 personnes, 9,531 hommes et 922 femmes. Les matériaux sont considérés représentatifs des villes et des régions agglomérées de la Norvège méridionale. A la suite d'examinations minutieuses on a trouvé chez les hommes 1.2  $\pm$  0.1 % et chez les femmes 0.8  $\pm$  0.3 % de syphilis séropositive. La distribution sur les groupes d'âge ressort des tables 3 et 6. Plus de la moitié ont indiqué qu'ils ignoraient leur maladie. Par une examination ordinaire on n'a pu constater des symptômes cliniques de la maladie que chez très peu de personnes. La plupart de ceux qui se savaient malades avaient obtenu un traitement insuffisant (table 5). On fait ressortir l'importance qui s'attache à dénicher autant que possible de ces cas de syphilis ignorée et à leur ménager du traitement; et des directives sont données à ce sujet.

### Zusammenfassung.

Die Häufigkeit seropositiver Syphilis in Norwegen bei präsumtiv gesunden Erwachsenen: Insgesamt sind 10,453 Personen, 9,531 Männer und 922 Frauen, untersucht worden. Das Material wird als repräsentativ für Städte und städtisch bebaute Gegenden in Süd-Norwegen angesehen. Nach eingehenden Untersuchungen wurden bei Männern 1.2  $\pm$  0.1 % und bei Frauen 0.8  $\pm$  0.3 % seropositiver Syphilis gefunden. Die Verteilung auf Altersgruppen geht aus Tabelle 3 und Tabelle 6 hervor. Mehr als die Hälfte der untersuchten Personen gab an, dass sie von ihrer Krankheit nichts

wüssten. Bei gewöhnlicher Untersuchung konnten klinische Symptome der Krankheit nur bei sehr wenigen nachgewiesen werden. Die meisten derer, die von ihrer Krankheit wussten, hatten eine ungenügende Behandlung erhalten (Tabelle 5). Es wird betont, dass es von Bedeutung ist, möglichst viele dieser Fälle unerkannter Syphilis aufzuspüren und sie entsprechender Behandlung zu unterziehen, und es werden Richtlinien hierfür angegeben.

### Literature.

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## **Boeck's sarcoid, experimentally produced by virulent, human tubercle bacilli in a case of Schaumann's disease.**

By

**L. E. WARFVINGE,**

(Submitted for publication March 2, 1943).

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In 1914, Schaumann proved that the skin affections described earlier, viz., Boeck's sarcoid and Besnier's lupus pernio, were merely symptoms of a general disease which may affect most of the organs of the body. Lymphogranuloma benignum (L. B.) was the name suggested by Schaumann for this illness. The disease is characterized as follows:

1) Specific histological changes, consisting of epithelioid cell tubercles without necrosis or caseation. Only a few giant cells or none at all, and an insignificant lymphocyte reaction in the surroundings. Exudative and polymorphonuclear cells are lacking. The changes can be restored by means of hyalin degeneration.

2) The disease is spread in the organism by hematogenous dissemination.

3) The disease has special affinity with the lymphoid tissue, the lungs, the skin, the bone medulla and the uvea. However, it also occurs in the spleen, the liver, the salivary and the lacrimal glands. The specific changes have, in certain cases, been said to appear in the kidney, the uterus, the heart, the skeleton musculature and in the central nervous system.

4) The hematological expression for the monocyte proliferation which leads to the epithelioid cell tubercles is a more or less

pronounced monocytosis. However, this only occurs during active proliferative phases.

5) A marked discrepancy between the anatomical extension of the disease and its deficiency in symptoms.

6) A pronounced tendency towards tuberculin anergy.

7) The disease is chronic and periodically recurrent. It is resistant to treatment, but may, nevertheless, at times heal spontaneously.

The etiology of this disease has been the subject of many speculations. However, a satisfactory elucidation has not as yet been achieved. The histo-pathological picture most closely corresponds to that of tuberculosis, notwithstanding the absence of necrosis. Tubercle bacilli have, in certain cases, been found earlier in histological sections. In 1941, Schaumann and Hallberg reported that they had succeeded in finding certain acid-fast bacilli in lymph glands in L. B., by means of »Nachtblau» staining. The number of positive inoculations of L. B. material on guinea-pigs is exceedingly small. In a critical literary survey, in 1938, Pinner found 25 cases of L. B., giving a positive guinea-pig test. However, almost all the positive animal inoculations disclosed a slow, progressive disease with atypical section findings. Or else, positive results were obtained only after repeated animal passages, a spontaneous infection in these cases being hard to avoid. Kyrle's observations from a case of Boeck's sarcoid give an explanation of the difficulties encountered in efforts to ascertain tubercle bacilli in L. B. During an acute phase, tubercle bacilli could be ascertained in the blood by means of guinea-pig tests. Biopsy of skin changes, a few days old, revealed unspecific inflammation and an abundance of acid-fast bacilli. Renewed biopsy, five weeks later, showed typical L. B. tissue, in which acid-fast bacilli could no longer be ascertained. These observations argue the point that tubercle bacilli can only be found during a short initial phase, before the specific L. B. tissue has had time to develop.

Important arguments for the tuberculous etiology are advanced, partly, by the, at present, not so few cases revealing a development of L. B. into a classic caseating, tuberculosis, and, partly, by the discovery of a simultaneous occurrence of L. B. and classic tuberculosis in the same organ, together with fluctuating communications between the two (Mylius and Schürmann). In this connection, it is of interest to keep in mind the phenomenon first

observed by Schaumann, viz., that the skin changes are restored when an L. B. patient has developed a classic tuberculosis and the tuberculin anergy has become an allergy. This phenomenon is, therefore, analogous to the well-known fact that lupus changes and skin tuberculides often are restored during the development of a caseous disintegration of organ tuberculosis.

The tuberculin anergy in L. B. is not comparable to the anergy in the acute infectious diseases, which is relative and of short duration. In L. B. the tuberculin anergy is often total and not even the largest tuberculin doses, administered intracutaneously (even undiluted tuberculin has been employed), produce any reaction. The antibodies, i. e. anticutins, discovered, in certain cases, in the blood of L. B. patients, which react to tuberculin and prevent its cutaneous reaction, do not seem to be specific and lack diagnostic value (Hämel). The anergy is, apparently, an essential etiological property in L. B., since this disease, evidently, only appears in the immune-biological conditions which are incompatible with caseous disintegration, i. e. tuberculin anergy.

Lemming was the first to attempt to analyse more closely the tuberculin anergy in L. B. (1936—1942). In order to find out, whether absolute anergy in L. B. occurs in an individual not infected with tuberculosis, or a positive anergy is prevalent in a special form of tuberculosis, Lemming suggested B. C. G. vaccination of patients suffering from L. B. which had been subjected to pathological-anatomical verification. If the sick persons were absolutely anergic and, therefore, had not been infected earlier with tuberculosis, they should, after B. C. G. vaccination, become tuberculin positive. On the other hand, if positive anergy occurred, perhaps, a somewhat different mode of reaction might be expected. In his first case, Lemming obtained, after intracutaneous injection of 0.15 mg bacilli, a local skin affection and regional adenitis. But, at a tuberculin test, 8—15 weeks after the inoculation, the patient was still tuberculin negative (up to 10 mg Mantoux). The regional adenitis was excised and, at a histological examination, revealed the picture of a typical and, in all probability, fresh L. B. Later, in a number of cases, Lemming has shown that tuberculin anergy in L. B. is not influenced by B. C. G. vaccination. In a case, published in 1942, describing a patient who was tuberculin negative and suffered from lupus pernio, Lemming gave an intracutaneous in-

jection of 0.1 mg bacilli. After a month, a small red infiltration appeared locally, and, after another few months, it had grown considerably and disclosed a bluish-brown, somewhat elevated surface with telangiectasia and white milia. Macroscopically, the skin infiltration corresponded to that of Boeck's sarcoid. Moreover, the microscopic examination showed a typical picture of L. B. The patient continued to remain negative.

These unusual reactions to B. C. G. vaccine, viz., in the first place, the non-appearance of tuberculin allergy, and, secondly, the formation of L. B. tissue locally or in the regional lymph glands, are of the greatest interest in connection with the question of the tuberculous etiology of the disease

An experimental contribution to the discussion of the etiology of L. B. has also been offered by Kveim, in a preceding report, in 1941. On account of the comprehensive material of negative inoculation tests in L. B., collected by the Skin Department of the Rikshospital in Oslo, the theory of the tuberculous etiology of the disease has been abandoned. In its place another hypothesis, forming the base of investigation, has been put forward, i. e. the possibility of the affection being an infectious disease *sui generis*.

Accordingly, from the fact that in lymphogranuloma inguinale a specific antigen from an affected gland can be formed which will give a specific cutaneous reaction, an antigen was prepared of a gland from a patient suffering from active Boeck's sarcoid. This glandular antigen was then applied intracutaneously to patients suffering from Boeck's sarcoid. Within a period of 1—4 weeks, a local bluish-brown or bluish-red infiltration appeared. In some cases this infiltration resembled a small sarcoid nodule. The infiltration was found, in a histological examination, to have a structure corresponding to that of L. B. No reaction occurred in a control material, comprising patients with tuberculosis and lues. There could be no question of a special reaction type in the L. B. patients to diverse unspecific antigens, since the Frei-reaction in all the cases turned out negative. Kveim is of the opinion that this is a specific, allergic reaction on a specific antigen.

The occurrence of an allergic reaction, such as Kveim has propounded, is, in all probability, unlikely, since it has taken the reaction between 1 and 4 weeks to appear. On the other hand, it seems possible, in the light of Schaumann-Hallberg's ascertain-

ment of acid-fast bacilli in L. B. glands, that Kveim's glandular antigen might contain certain atypical and avirulent tubercle bacilli. These bacilli should produce local changes similar to those obtained by Lemming with B. C. G. Thus, Kveim's specific reaction in Boeck's sarcoid does not seem to support his hypothesis, viz., that Boeck's sarcoid is a disease *sui generis*.

It has long been known that tuberculosis among some animals (viz., mice, rats and cats) discloses the same biological and morphological characteristics which distinguish L. B. from classic tuberculosis. Accordingly, white rats are almost immune to tuberculosis (Jadassohn). Several authors have shown that large doses of human or bovine tubercle bacilli (1 mg. and more) in rats only produce purely productive changes, i. e. epithelioid cell tubercles without necrosis, with a few giant cells or none at all and, for the most part, without lymphocyte infiltration in the surroundings. These tubercles never disintegrate, but they can be restored by fibrosis. *Tuberculin allergy never occurs, in spite of the survival of the tubercle bacilli which maintain their virulence.*

The reaction of the animals to tuberculous infection consists of a strong local increase of the elements of the macrophage system. This intensification of the activity in the reticulo-endothelial system is produced in the white rat by a latent infection of *Bartonella muris ratti*, which infects all laboratory rats. In an experimental work, Kallós has convincingly demonstrated the significance of the *Bartonella* infection to the course of the tuberculous infection in the white rat. Kallós treated white rats with an arsenic-antimony preparation by means of which the *Bartonella* infection was checked. Then, the rats were isolated and besprinkled daily in order to destroy the lice which transfer the infection. After that, spleen extirpation was performed and, in order further to restrict the reticulo-endothelial system, Indian ink was administered intravenously and intraperitoneally. Then human, virulent tubercle bacilli were injected intraperitoneally. All the rats died within 10 weeks, and at autopsy all of them revealed a classic tuberculosis with typical caseous disintegration within the tubercles. The control rats, who had only been relieved of the *Bartonella* infection, while the reticulo-endothelial system had not been blocked, disclosed the usual rat-tuberculosis with epithelioid cell tubercles with absence of necrosis.





Fig. 1. X-ray 17. 4. 39. Large glands in hili and paratracheally.

Thus, no tuberculosis immunity occurs in rats. Instead, the special conditions of the tuberculosis infection are due to the stimulation of the macrophage system by the Bartonella infection. Kallós' experiments offer a good demonstration of the decisive part played by the functional state of the macrophage system on tuberculosis allergy and the course of the tuberculosis.

The experimental work by Lemming, Kveim and Kallós, referred to here, has given new and important support to the contention that tuberculosis and L. B. are two different phases of one and the same disease.

An additional contribution to the etiological discussion is obtained in a case described below. Here, it has been possible to produce Boeck's sarcoïd by intracutaneous injection of virulent, human tubercle bacilli in a patient, suffering from L. B. and patent pulmonary tuberculosis.

The patient is a woman of 26 years of age, who has earlier been healthy, without exception. No heredity or exposure to tuberculosis. In March, 1939, both the salivary glands of the ears began to swell, without any feeling of illness, or fever. Simultaneously, pronounced reddening and chafing of the left eye. The right eye was also slightly irritated. No coughing or stitch.

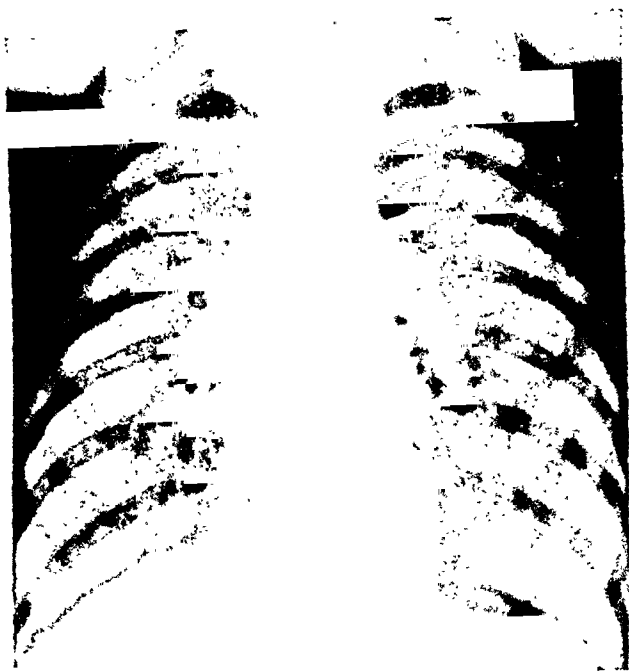


Fig. 2. X-ray 28. 10. 41. The lymphoma shadows remain, but now extended, small-spotted densities within both lung fields have been added.

She was admitted to the Medical Department of Östersund's Lasarett on 14. 4. 1939, with the diagnosis of febris uveoparotidea.<sup>1</sup>

Her general condition was good and she was altogether unaffected. Subfebrile temperature. She had firm, swollen parotid glands on both sides which were not sore and of the size of a thumb. A couple of firm, inflamed glands, the size of beans, were found preauricularly and a few, the size of grains, in the groin. The state of the eyes revealed a fine wave of light in the left one, and a group of relatively large precipitates in the lower part of the cornea. Fine cloudnings of the vitreous body. The right eye was free from irritation. (Kjellner). No neurological remarks. Lumbar puncture: 6 mononuclear cells/mm<sup>3</sup> and negative albuminous reactions. S. R.: 13mm/1 hour. Mantoux 0.1 mg negative while 1 mg gave a faint reaction (8 × 10 mm) X-ray of the chest (Fig. 1) showed hilum glands on both sides, the size of a walnut, and a large paratracheal gland on the right side. A few distinctly outlined, streaked dense areas below the left hilum (Gräberger). Test excision from the parotid gland and a lymph gland revealed typical L. B. tissue. No tubercle bacilli were found in the sections. (Wahlgren).

The parotid glands were treated with röntgen and soon recovered. The state of the left eye improved owing to atropin treatment. Since the summer of 1939, the patient has been free from symptoms.

<sup>1</sup> The author wishes to express his gratitude to the Medical Superintendent, Dr. I. Lundholm, for his permission to publish excerpts from the Journal.

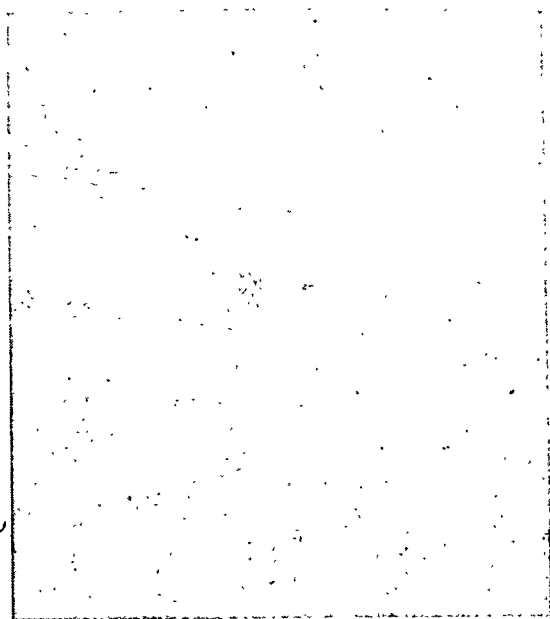


Fig. 3. The skin lesion four weeks after the inoculation of the tubercle bacilli.

In June 1941, the patient fell ill with acute fever, bad coughing and abundant expectoration. The coughing continued even after the temperature had gone down, and she was out of breath. Accordingly, she called at the Central Dispensary in Solliden on 28. 10. 1941. X-ray (Fig. 2) showed within the upper  $\frac{2}{3}$  of both pulmonary fields extended, small, flocky, partly confluent, indistinctly circumscribed densities. Small cavity centrally on the left side was suspected. As before, the lymphoma shadows appeared in hili and paratracheally. On 5. 11. 1941 tubercle bacilli were ascertained in the sputum and the patient was admitted to the Solliden Sanatorium 22. 11. 41.

The patient was then in a comparatively good general condition. Still she had lost considerable weight and had a subfebrile temperature. The superficial lymph glands were generally enlarged. On the throat, in the axillae and in the groins, a number of glands, the size of peas, were found, and glands, the size of beans, were observed in both fossae supraclav. Otherwise, negative somatic state. S. R.: 58 mm/1 hour. White blood corpuscles: 9700, 22 % of which were monocytes, 15 % lymphocytes, 1 % basophile, 4 % eosinophile, 7 % rod-nuclear and 51 % segment-nuclear. Mantoux 0.1 and 1 mg utterly negative. Mantoux 3 mg was also negative (infiltration  $5 \times 5$  mm). Total albumen in the serum: 7.84 %, 4.22 % of which were albumens and 3.62 % globulins. X-ray of the chest showed unchanged condition. X-ray of the hand and foot skeleton disclosed no cystic changes. Abundance of tubercle bacilli in the sputum. Guinea pig test with the sputum showed that the bacilli were virulent for these animals.

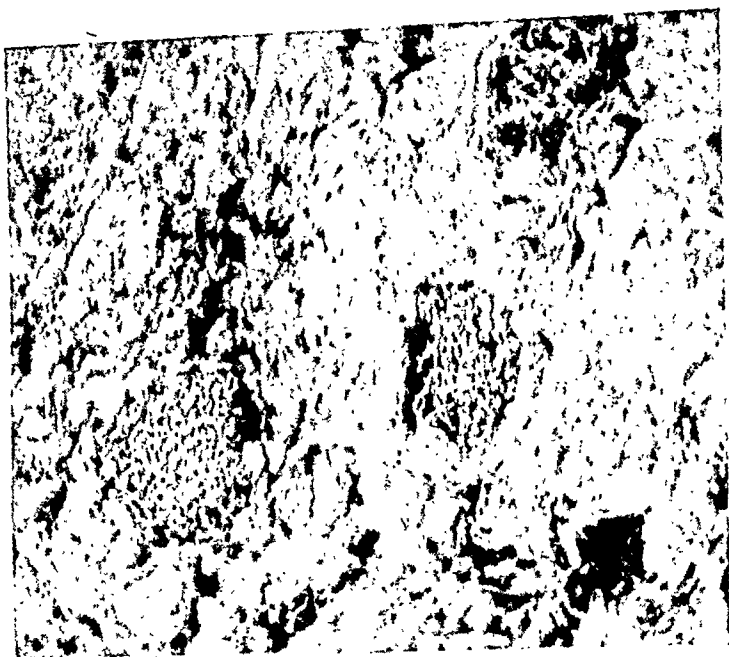


Fig. 4. Section of the lesion. In the corium epithelioid foci sharply circumscribed, absence of necrosis and of peripheral lymphoid reaction.

Sputum was cultivated on Löwenstein substrate and then sent to The Sahlgren Hospital, the Bacteriological Laboratory, for type specification. Virulent, *human* tubercle bacilli were ascertained (A. Wassén). A sterile suspension was then made from the Löwenstein culture. This was diluted with physiological sodium chloride until a dilution of between 10 and 100 tubercle bacilli per 0.1 cm<sup>3</sup> was obtained. The sterility of the solution was controlled by means of repeated cultures on common substrates. 0.1 cm<sup>3</sup> of the bacterial suspension was injected intracutaneously into one of the patient's thighs. After 6 days, an insignificant brown-red infiltration was noticed locally, which slowly grew and attained the size of a large peppercorn after 4 weeks (Fig. 3). The infiltration appeared like a bluish-brown-red, distinctly elevated, firm papilla, with an even surface and sharply circumscribed against its surroundings. At diascopy it took on a yellowish-brown colour. No reddening or infiltration in the surroundings. No reaction from the regional lymph glands.

The skin changes were excised a months after inoculation. The histological preparations (which, unfortunately, happened to be in the periphery of the macroscopical changes) disclosed sharply

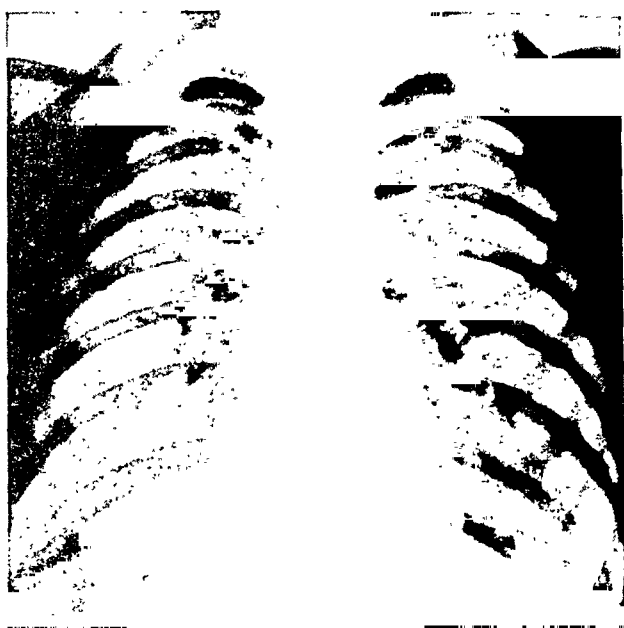


Fig. 5. X-ray 22. 8. 42. Regress of the small-spotted densities and the lymphomas. Signs of extended fibrosis remain.

circumscribed epithelioid cell accumulations in corium, absence of necrosis and giant cells (Fig. 4). No lymphocyte infiltration in the surroundings. Tubercle bacilli could not be ascertained in the sections (Wahlgren).

The patient now proceeded to improve gradually. She became afebrile, increased in weight and the S. R. fell. Since January 1942, she has remained free from bacilli. At the discharge on 13. 6. 42, her general condition was excellent, she had increased 11 kg in weight and her S. R. was 21 mm/1 hour. Mantoux 0.1 and 1 mg negative, while Mantoux 3 mg gave an infiltration of  $10 \times 12$  mm., i. e. definitely positive. X-ray showed distinct regress of the small-spotted parenchymal densities. At a control examination on 22. 8. 42, S. R. was found to be 17 mm/1 hour and the radiogram (Fig. 5) showed continued regress. The small-spotted densities had disappeared and only distinctly outlined, streaked and net-like dense area remained. No lymphoma shadows ascertainable.

This patient, who suffered from L. B. as well as patent pulmonary tuberculosis, presented a rare opportunity for an experimental demonstration of the etiological significance of the tubercle bacillus in L. B. The cultures and animal tests showed that sputum contained virulent, human tubercle bacilli. Within a month, at intracutaneous injection, a sterile suspension of these bacilli gave

macro- and microscopical changes which corresponded with Boeck's sarcoid. This productive reaction is extremely noteworthy, since, according to »Koch's Grundversuch», inoculation of virulent tubercle bacilli in an individual earlier infected, always otherwise leads to local necrosis within a few days which is soon checked, leaving a superficial ulcer which is rapidly and permanently healed.

The present investigation is the first to prove that virulent, human tubercle bacilli in man can produce purely productive changes, corresponding to L. B.

The name Lymphogranuloma benignum suggested by Schaumann could be replaced by the term »non-caseating tuberculosis» which is commonly accepted in the anglo-saxon literature, or by »storpide sklerosierende Tuberkulose», as used in the German literature.

### Summary.

Lemming has, by means of B. C. G. vaccination, shown that a positive anergy against tuberculin exists in L. B. and that B. C. G. can produce local changes of typical L. B. appearance.

Kveim's result shows that the antigen prepared on L. B.-gland forms specific cutaneous reactions of the L. B. type in patients suffering from L. B. The possibility that the glandular antigen contains avirulent tubercle bacilli may be considered great in the light of Schaumann-Hallberg's investigations.

Kallós' experiments on animals show that virulent tubercle bacilli can cause L. B.-changes in animals by special stimulation of the reticulo-endothelial system, owing to a latent infection. If this is removed an ordinary disintegrating tuberculosis is developed.

The present author has in a patient suffering from simultaneous L. B. and patent pulmonary tuberculosis produced local changes of typical L. B. appearance, by means of intracutaneous injection of the patient's own, virulent, human tubercle bacilli.

These experiments justify the conclusion that L. B. and tuberculosis are two different phases of one and the same disease.

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## On the Determination of Perabrodil (Diodrast) in Plasma and Urine.

By

BØRGE BAK, CLAUS BRUN and FLEMMING RAASCHOU.

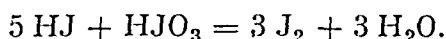
(Submitted for publication January 28, 1943.)

In 1937 Smith, Goldring & Chasis (1) introduced a method for employing Perabrodil (diodrast) in determining the total flow of blood through the kidneys (the diodrast clearance) and the quantity of active tubulus tissue ( $T_m$  = tubular excretory mass). From this and other works it appears that by one passage through the kidneys the blood is freed almost completely of diodrast at plasma concentrations of less than 5 mg % diodrast iodine. Thus the diodrast clearance is practically identical with the total blood flow.

It would be desirable to have a reliable method of determining the diodrast iodine in plasma and urine, if possible one capable of being used clinically. Having this latter desideratum in mind one must avoid the use of methods which take much time, complicated incineration processes, distillations or the like [Kendall (2), Billmann (3), Mathews, Curtis & Brode (4) (5)]. From a clinical point of view it would be desirable to have a method in which the iodine analysis proceeded so to say in a test-tube. This requirement was met when White & Rolf (6) in 1940 published a micro method for determining diodrast-iodine.



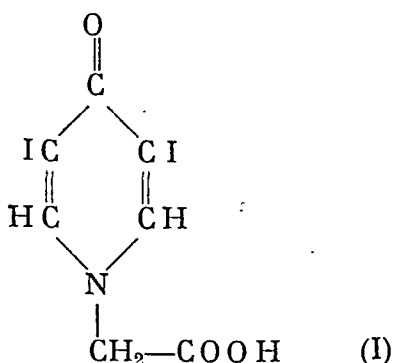
The principle of their method is this: Under the influence of potassium permanganate and sulphuric acid diodrast is oxydized at 90—100°, so that at the end of the process iodine is present in the form of iodate. A considerable excess of potassium permanganate is employed in this oxydizing process, and this is reduced to manganocompounds by the addition of sodium nitrite, whereafter the excess of nitrite is reduced by the addition of urea. Then follows cooling to 10—20° and the addition of a potassium iodide crystal. This potassium iodide then reacts in the acid solution with the diodrast-iodine (present in the form of  $\text{HJO}_3$ ) according to the equation:



This manipulation gives the advantages deriving from the fact that six times the quantity of iodine present as diodrast iodine has to be determined.

Unfortunately, White & Rolf seem not to have tested their method thoroughly. This appears already from the circumstance that soon afterwards they published a paper (7) in which the method was altered considerably. The course now was to oxydize the diodrast in a basic solution, but at the same time a much longer period was necessary for the potassium permanganate to act on the diodrast. Furthermore, the method lost something of its practical usefulness by the boiling time being made dependent on the diodrast content of the analysis. As we believed that White & Rolf's first publication contained a useful basis for a method of determining diodrast-iodine, we determined to put the matter to a thorough test.

Diodrast is a white crystalline substance which chemically is a salt of Diaethanolamin:  $[\text{NH} (\text{CH}_2\text{CH}_2\text{OH})_2]$  and the acid: 3,5-diiodo-4-pyridon-N-acetic acid:



The iodine percentage of this substance is 49.8. Diodrast is soluble in water with a neutral reaction. In Denmark it is obtainable only in aqueous solution (Bayer's Perabrodil, 35 % and 50 %). These solutions are widely employed for intravenous urography, but of course cannot directly be employed as stock solutions in an analytical work. We have therefore made a close examination of Bayer's Perabrodil (35 %).

In a crystallization dish 47.4 g. Perabrodil solution was exposed for evaporation at room temperature. After final desiccation in a vacuum exsiccator over  $P_2O_5$  to constant weight the evaporation residue weighed 14.6 g. The weight percentage of the Perabrodil solution had therefore been 30.9. The specific gravity of the solution at  $20^\circ$  is: 1.170; its strength in g/100  $cm^3$  is therefore 36.2 at  $20^\circ$ . On the ampulla the strength is stated to be 35 %.

Part of the evaporation residue (II) was dissolved in water, whereafter hydrochloric acid was added. This caused a crystalline precipitate which, as one would expect, was the acid (I). That this was the case was proved by the following analyses: 0.3459 g of the substance was titrated with 8.50  $cm^3$  0.0997 n NaOH. The acid equivalent was thereby found to be 408 (theoretically: 405); 0.2271 g of the substance was treated according to Baubigny & Chavanne's method for determining iodine in organic substances. The AgI given off weighed 0.2635 g. Therefore the iodine equivalent is: 203 (theoretically 202.5). The melting point of the acid was found to be  $248^\circ$  in conformity with the literature (9).

Next the iodine equivalent of the evaporation residue (II) was determined by the same method. Analyses: 0.5664 g substance gave 0.5229 g AgI. Iodine equivalent: 254 (theoretically: 254). We conclude from these analyses that the evaporation residue of the Bayer preparation is practically pure Perabrodil. Finally, we have found that with the analysis-technique to be described later Bayer's Perabrodil solution gives the same results as a diodrast solution prepared by us; the latter was procured by mixing equimolar quantities of acid (I) and analytically pure diaethanolamin.

We then proceeded to test White & Rolf's method on aqueous diodrast solutions. It was quickly found that reproducible results were not obtained with complete regularity. In order to get reliable analysis results we then made a careful test of each of the stages in the procedure described by White & Rolf. (W. & R.)

1) In conformity with W. & R. we added 0.3  $cm^3$  of a saturated  $KMnO_4$  solution and 0.1  $cm^3$  of 4 m  $H_2SO_4$ , which represents an ample excess.

2) The boiling time with  $KMnO_4$  is given as 10 minutes by W. &

R. In a number of analyses we examined the influence of the length of the boiling time, and it was found that 10 minutes is just sufficient and that longer boiling (15 to 20 minutes) has no deleterious effect on the result of the analysis.

3) The amount of nitrite, which W. & R. state is variable from one analysis to another, may be made constant:  $0.4 \text{ cm}^3$  1 m sodium nitrite, which is added all at once to the analysis over the boiling water-bath. The sodium-nitrite solution is added direct to the solution with a micro-pipette (and not by dropping), thus avoiding the chance of splashing the nitrite up the walls of the tube.

4) According to W. & R. the nitrite treatment lasts two minutes; as nitrite may have a reducing effect on iodate, it was of interest to ascertain what role is actually played by the period of nitrite action. By experiment we found that there was no reduction of the iodate, even when the time was prolonged to 15 minutes. This means that one can have a larger number of analyses going than W. & R. suggest.

5) Next, it is a condition of the correct completion of the analysis that the nitrite excess is eliminated completely. We found that this can be done quite reliably by adding  $1 \text{ cm}^3$  of 5 m urea solution.

6) The analysis is then boiled, being vigorously shaken repeatedly to ensure that the walls of the tube everywhere are wetted with the fluid. Boiling is continued until no more gas is given off, which takes about three minutes. Longer boiling does not affect the result of the analysis; this is of importance when reduced volume is desirable having regard to the subsequent titration.

7) According to W. & R. the analysis is now cooled down to 10 to  $20^\circ$ . At this point we prefer to follow Biilmann's instructions (3), titrating at  $0-5^\circ$ ; the endpoint of the titration is most marked there.

8) The quantity of potassium iodide to be used for titration is stated by W. & R. in their first work (6) as «a few crystals». In the second publication (7) the quantity is specified in more detail at 0.5 mg. We work with a freshly made solution of potassium iodide (2 g in  $3 \text{ cm}^3 \text{ H}_2\text{O}$ ); of this  $0.1 \text{ cm}^3$  (= 55 mg potassium iodide) is added for about  $4 \text{ cm}^3$  titration volume. By this means we obtain about the same potassium-iodide concentration every time. As we were able to show, the concentration of potassium-iodide is of

importance to the result of titration: if various quantities of the potassium-iodide solution are added to analyses containing the same quantity of  $\text{KJO}_3$  in 4  $\text{cm}^3$  water we get too low a titre if the quantity of potassium-iodide is less than 0.05  $\text{cm}^3$  (= about 30 mg). On the other hand the quantity of potassium-iodide must not be too large, as otherwise there is a risk of atmospheric oxydation.

9) The blue colouring (air oxydation) generally developing shortly after the endpoint of a starch titration was not seen at all under our conditions; the analyses were colourless even half an hour after titration was completed.

Hence the actual procedure in carrying out the analysis is this:

The solution, of which the diodrast-iodine content should be about 10 Gamma iodine, is poured into a cylindrical test-tube (measurements:  $3 \times 10$  cm). Then add 0.3  $\text{cm}^3$  saturated potassium permanganate and 0.1  $\text{cm}^3$  4 m sulphuric acid. It is then given 10 minutes in a boiling water-bath, whereafter 0.4  $\text{cm}^3$  1 m sodium nitrite is added with a pipette, taking care not to splash the nitrite up the walls of the test-tube. Shake until any deposit of manganic dioxide ( $\text{MnO}_2$ ) is completely removed. Now add 1  $\text{cm}^3$  5 m urea. Shake vigorously and continue boiling in the water-bath until no more gas is given off (about 3 minutes). Cool in ice-water. After complete cooling add 0.1  $\text{cm}^3$  potassium iodide (freshly prepared: 2 g potassium iodide in 3  $\text{cm}^3$   $\text{H}_2\text{O}$ ) and 0.5  $\text{cm}^3$  0.2 % starch solution (a. m. Sulkowsky (Merck)). The resulting iodine is titrated with sodium-thiosulphate solution. For an iodine content of less than 20 Gamma use 0.005 n sodium-thiosulphate (0.1200 g/L). If the iodine content is over 20 Gamma, use 0.002 n sodium-thiosulphate. For preparing sodium-thiosulphate we used thoroughly boiled water, and it was stabilized by adding carbonate of sodium (0.2 g per litre). This sodium-thiosulphate has had an almost constant titer for six months.

We employ a 2  $\text{cm}^3$  burette graded in 1/100th  $\text{cm}^3$ . Titration proceeds in artificial light against a white background.

In this manner 20 analyses can easily be handled at once.

With the use of this technique we have made numerous blind analyses without finding any blind value. By this means we ensured that none of the reagents we used contained a trace of iodine, and at the same time it was confirmed that e. g. the removal of sodium nitrite with urea was complete.

It was also found that tobacco smoke and iodine accidentally present in the atmosphere (as in an ordinary hospital laboratory) had no effect when using the method (in contrast to Biilmann's method (3), in which about 10—100 times smaller amounts of iodine are determined).

We shall now proceed to prove the usefulness of the method, in connection with which we have tested:

- A) Aqueous potassium iodide solutions.
- B) Aqueous diodrast solutions.
- C) Deproteinized plasma + aqueous diodrast solutions.
- D) Plasma + aqueous diodrast solutions.
- E) Urine + aqueous diodrast solutions.

A) Of an aqueous potassium iodide solution containing 15.7 gamma iodine per  $\text{cm}^3$ . 1  $\text{cm}^3$  was analysed by the above method. The mean value of five analyses was: 15.3 gamma iodine (97.5 %). The greatest mutual deviation was 3 %.

B) By dissolving 0.7965 g acid (I) and 0.1998 g diaethanolamin (equimolar quantities) in 1 litre of water we obtained a diodrast solution, which was diluted 50 times. The diluted solution contains 9.92 gamma iodine per  $\text{cm}^3$ . In 5 determinations, which mutually deviated less than  $\frac{1}{2}$  % from one another, we found 9.99 gamma iodine (101 %).

In the same manner we weighed off 0.9981 g of the evaporation residue (II) from Bayer's Perabrodil; it was dissolved in 1 litre of water and then diluted 50 times. The diluted solution contained 9.94 gamma iodine per  $\text{cm}^3$ . In 5 determinations, which mutually deviated less than 1 % from one another, we found 10.04 gamma iodine (101 %).

We then proceeded to test the range of the method in respect of aqueous diodrast solutions. It turned out that one must reckon with having to determine from 2 to 60 gamma diodrast iodine in one analysis. The following table gives our results:

Added gamma diodrast iodine:	1.988	3.976	9.941	19.88	29.82	39.76	59.65
Found gamma iodine: . . . . .	2.18	4.16	10.04	19.50	29.48	38.56	59.11
Found iodine percent.: . . . . .	110.0	105.0	101.0	98.2	98.8	97.0	98.9
Greatest mutual deviation (%):	10.0	4.0	2.0	2.0	3.0	2.0	1.0

These analyses are the mean values of 5 determinations. The standard deviation of 32 diodrast analyses (10 gamma diodrast iodine) was  $\pm 0.14$  gamma diodrast iodine.

C) Deproteinizing of plasma according to W. & R. is carried out by adding 3 volumes of 7 % trichloroacetic acid to 1 volume of plasma and 6 volumes of  $H_2O$ . With this the concentration of trichloroacetic acid at the moment of precipitation is 2.1 %; according to Peters & van Slyke (8), however, protein precipitation should take place at a trichloroacetic acid concentration of 4.5—9 %. If we precipitate according to W. & R. it proves to be impossible, even after standing 15 minutes and 15 minutes centrifuging (3500 revolutions per minute), to get a clear filtrate. If then an equal volume of trichloroacetic acid (20 %) is added to the «filtrate» from W. & R.'s protein precipitation, the opalescence of the analysis increases greatly, showing that the protein precipitation was insufficient.

To a filtrate secured according to W. & R. we added 3 cm<sup>3</sup> diodrast solution (containing 31.7 gamma diodrast iodine). We recovered 87.5 % of the quantity of diodrast iodine added.

We then prepared a filtrate by precipitating with equal parts of 20 % trichloroacetic acid. When the same quantity of diodrast as in the above experiment was added, the result was surprising, in that no iodine was recovered at all.

This means that an increase of the trichloroacetic acid concentration for the purpose of ensuring complete protein precipitation fails in its object with the analysis technique described. In our opinion the reason is that trichloroacetic acid has a reducing effect on iodate — which in fact we have directly confirmed — and therefore in selecting another protein precipitant we made it a condition that it should not be oxydisable by iodate.

The reagent we chose was sodium wolframate — sulphuric acid [Haden's modification of Folin—Wu's protein precipitation (8)]: To 1 cm<sup>3</sup> plasma we added 1 cm<sup>3</sup> of 10 % sodium wolframate and 8 cm<sup>3</sup> N/12 sulphuric acid. Centrifuging gives a clear filtrate. For the further iodine analysis we used from 1 to 7.5 cm<sup>3</sup> of the plasma filtrate thus obtained.

To this filtrate we added 3 cm<sup>3</sup> diodrast solution (containing 31.7 gamma diodrast iodine). We recovered 98 % iodine. (When we used trichloroacetic acid we found 87.5 %).

If it is desired to determine quantities of diodrast below 5 gamma it is advisable to dilute the plasma for example only 5 times: 2 cm<sup>3</sup> plasma, 2 cm<sup>3</sup> 10 % sodium wolframaté, 2 cm<sup>3</sup>  $\frac{2}{3}$  N Sulphuric acid, 4 cm<sup>3</sup> water, corresponding to the above demonstrated inaccuracy at the low diodrast values.

D) We then tested the applicability of the method on plasma containing diodrast. Smith, Goldring & Chasis (1) state that the diodrast concentrations at which the diodrast clearance is determined lie between 5 and 0.5 mg % diodrast iodine (50—5 gamma/cm<sup>3</sup>), and that the determination of diodrast-T<sub>m</sub> proceeds at diodrast-iodine concentrations between 15 and 50 mg % (150—500 gamma/cm<sup>3</sup>).

On adding diodrast to the plasma of various individuals W.&R. rather constantly found about 82 % diodrast coming through with the filtrate (6). In the later work (7) they found about 87 % very constantly.

Employing our own method (wolframate precipitation) we now added diodrast in various quantities to the plasma of different persons and to plasma dilutions.

On adding from 8 to 40 gamma diodrast iodine per cm<sup>3</sup> to the normal plasma of various persons we recovered an average of 90 % of the diodrast. In all we made 40 determinations, resulting in the recovery of from 87 to 94 % of the diodrast. The deviations from the 90 % seem to depend solely on the experimental individual, but in any case they are so small that it is necessary to determine them only when the greatest accuracy is required.

On adding from 8 to 40 gamma diodrast iodine per cm<sup>3</sup> to normal plasma diluted two to four times, it was found here again that very nearly 90 % was recovered. The circumstance that 90 % is recovered would thus seem — within the plasma-protein concentrations met with in practice — to be independent of the protein concentration.

E) In order to work with 10 to 20 gamma diodrast iodine per analysis the urine must generally be diluted 100—1000 times. With this dilution we, like W. & R., had complete recovery of all the diodrast added to normal urine. The same was found for albuminous urine diluted 100 times — without protein precipitation.

In conclusion we may say that the above method for determining diodrast in plasma and urine has come up to our expectations in the further investigations on which we are now engaged. Only rarely (in about 1 analysis out of 15) does it fail. This always happens in the same manner, an excessive quantity of free iodine being liberated when the potassium iodide is added — apparently due to incomplete removal of potassium permanganate or sodium nitrite. As a rule, however, these incorrectly made analyses are easily distinguished from the correct ones, as the quantity of iodine is much greater than what may be expected. As a safeguard against this uncertainty in the method we always make triple analyses.

### Summary.

A critical examination is made of White & Rolf's method of determining Perabrodil (diodrast) in plasma and urine.

A description is given of an analytical method whereby diodrast iodine can be determined in quantities from 6 to 60 gamma with an error of 3 %.

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## Hemochromatosis.

Case Report with Special Reference to Symptomatology and  
Pathogenesis.

By

BJÖRN KNUTSEN.

(Submitted for publication February 1, 1943).

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In the last few years we have in the Medical Department of the Drammen Hospital had two cases of hemochromatosis with special complications. In both cases hypersideremia was observed, which is of the greatest importance for an understanding of the pathogenesis of the disease.

### I.

#### *Case reports.*

**Case 1.** H. B. Journ. No. 6281 42/43.

Man, aged 39. Gardener.

During the last three years he has been several times admitted to the hospital.

His mother died of diabetic coma. Otherwise he knows of no case of diabetes in the family. His father and his brothers and sisters, 8 in all, as well as one child, are healthy and have no remarkable skin pigmentation. He himself has always been strikingly dark-skinned and has for that reason been called »the foreigner». In the summer of 1939 it seemed to him that his skin became much darker than ever before.

In July 1939 he got diabetes, with polydipsia, polyuria, emaciation, clouded vision, glycosuria and ketonuria. The symptoms rapidly abated on dietary treatment.

On admission to the hospital in September that year he had moderate glycosuria, slight ketonuria and a fasting blood sugar of 321 mg per cent. A remarkable pigmentation of the skin was at once noted, being most

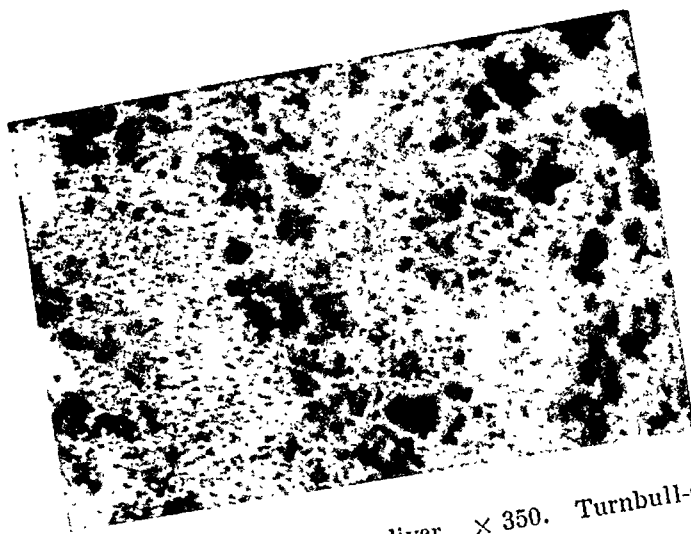


Fig. 1. Case 1. Punctate from liver.  $\times 350$ . Turnbull-staining.

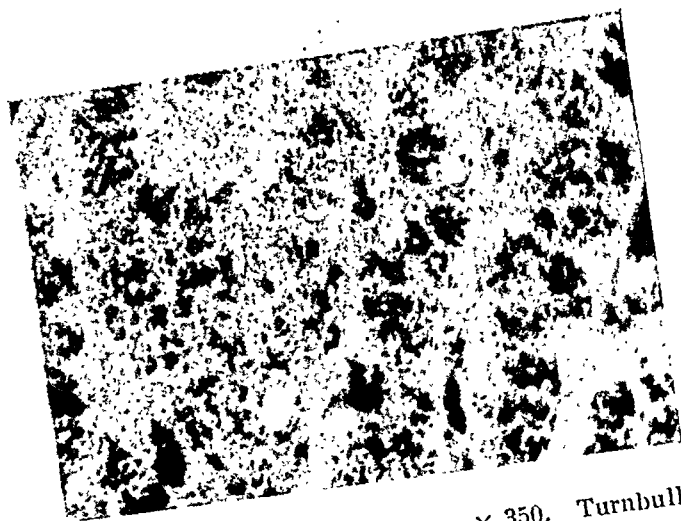


Fig. 2. Case 2. Punctate from liver.  $\times 350$ . Turnbull-staining

marked on the forearms and on the back of the hands, on the extensor side of the legs, on the face and around the genitals. The pigmentation was brownish, with a more bluish-gray tinge in the most intensely coloured regions. No pigmentation of mucous membranes. The liver was enlarged, firm and a little tender to touch, with a blunt lower edge reaching to about two finger-breadths below the costal arch. The spleen was not palpable. No distended veins were found over the abdomen and there was no ascites. Otherwise no pathological findings on examination of the organs.

His diabetes was kept in check by administration of insulin and for some time afterwards he felt well. But half a year after his first stay in the hospital he got cardiac troubles, which have thereafter been a marked feature of the clinical picture. He got pains in the chest and neck, pains which by degrees assumed the character of typical attacks of angina pectoris. In April 1940 he was again admitted to the hospital after a severe attack presenting clinical signs of cardiac infarction, with fever, increased sedimentation rate and electrocardiographic changes. On being kept in bed he soon became free from pain and when he left the hospital three months later there remained only small electrocardiographic changes and a slightly increased sedimentation rate.

His condition in the following two years was more or less uncharged, but he was weak, had little capacity for work and got angina pectoris on exertion. In May 1942 he was again admitted to the hospital after a violent attack of pains, once more presenting clinical signs of cardiac infarction. He was subfebrile, the blood pressure had fallen to 105/75 mm Hg and the sedimentation rate was 48 mm per hour. No pericardial friction rub was noted, but repeated electrocardiographic examinations revealed an infarction of the posterior wall. After lying in bed for six weeks he was free from pain and without fever, the sedimentation rate fell to 10 mm per hour and the blood pressure rose to the usual height.

He has since been comparatively well, works at small jobs, but gets pains after exertions. His general condition has been more or less unaltered and his weight was well maintained until last summer when he lost some few kilograms.

The skin pigmentation varies somewhat in intensity. He believes himself that his skin was darker during the first time he had diabetes. Periodically there appear on the otherwise deeply pigmented skin of the forearms, abdomen, penis etc. entirely white, unpigmented patches. These white patches and areas disappear again after some time.

He has not noticed any remarkable loss of hair. The hair on the head has for many years been very thin, but has not become more so since the clinical manifestation of the disease. The axillary and pubic hair remains intact. Complete sexual impotence has existed since the disease set in.

His diabetes has been of medium severity with little tendency to acidosis. A not inconsiderable degree of glycosuria was present during the whole time, but never ketonuric. With only two injections of insulin

per day the excretion of sugar could not be sufficiently reduced, because of a tendency to hypoglycemia. On the other hand, there was no resistance to insulin, such as has been reported in some cases of «bronzed diabetes». In the course of the more than three years his diabetes has lasted it has not shown any distinct progression.

Among the laboratory findings it may be mentioned that there has constantly been found a normal or very slightly increased icteric index and slight urobilinuria, findings which must be deemed to have connection with the cirrhosis of the liver. As a sign of hepatic insufficiency must also be regarded the severe hemeralopia noted in repeated tests.

The Takata test gave negative results. Determination of prothrombin in the blood showed normal values. Wassermann and Meinicke tests in serum were negative. In numerous examinations of hemoglobin, erythrocytes, reticulocytes and leucocytes normal values were found. A sternal puncture showed normal morphology and distribution. Thus there were found no signs of increased destruction, increased or reduced regeneration of the red blood corpuscles. Differential counts of the white corpuscles revealed normal conditions. Determination of the blood cholesterol at different times showed 320, 215 and 331 mg per cent, *i. e.* hypercholesterolemia. A determination of serum-iron May 1942 revealed a material increase, 225 gamma per cent. A control examination half a year later showed 197 gamma per cent.

From the finding of hypertrophic liver, bronzed pigmentation of the skin and diabetes it was assumed already during his first stay in the hospital to be a case of bronzed diabetes. A biopsy of the skin, however, revealed only a large amount of physiological, but no iron-containing pigments. September 1941 the diagnosis was verified by puncture of the liver. The microscopic picture (Fig. 1) shows liver tissue with some parenchymatous degeneration as well as a marked increase of stroma with fibrosis. There is seen an abundant deposition of dirty-brown pigment, mostly in the liver cells, where it occurs in fine granules, but also in the connective tissue, where it is more inclined to gather into lumps. The pigment gives positive reaction for iron on staining by the Turnbull method (iron-containing pigments bluecoloured). The histological diagnosis was hemochromatosis. Such a large quantity of hemosiderin in a cirrhotic liver could hardly be deemed compatible with any other diagnosis.

**Case 2.** L. L. Journ. No. 7149. 42/43.

Man, aged 54. Factory worker.

He has been treated in the hospital several times during the last 4 years. So far as he knows, there has been no case of diabetes or remarkably dark skin-colouring in his family. He has three children, all of whom are of pale complexion. In his younger years he was in America, where he worked for two years in a copper mine. In 1919 he returned to Norway and has since not been more exposed than others to the risk of copper poisoning.

He had not noticed any darkness of the skin before the present illness commenced in January 1938 with fracture of a rib, first on the right and afterwards on the left side, after remarkably slight injuries. Shortly afterwards he fell from a cycle and sustained a petrochantary fracture of the left thigh, for which he was treated in the surgical department.

In conjunction with these fractures he began to get pains of increasing severity in the lumbar and sacral regions of the spine, and it is chiefly from these pains that he has since been suffering, with shorter or longer periods of improvement.

On his admission to the hospital November 1938 attention was at once drawn to a striking pigmentation of the skin, of dirty-brown or more bluish-gray colour. The pigmentation was general and diffused, but was considerably more intense on the forearms, upper arms and extensor side of the legs, as well as on the face. There was also marked pigmentation over the back and abdomen and around the genitals. No pigmentation of the mucous membranes were noted. The abdomen was meteoristic. The liver was enlarged, slightly tender, of firm consistency, with a somewhat lumpy surface and a blunt lower edge extending 2 or 3 finger-breadths below the costal arch. The left lobe of the liver was particularly large, so that it felt like an enlarged spleen. But the spleen was not palpable. There were no distended veins over the abdomen and no ascites. Otherwise nothing of interest was found on examination of the organs, but arcuate kyphosis was noted in the thoracic and lumbar section of the spinal column.

In February 1941, three years after the first symptoms appeared the illness entered into a new phase, as he got diabetes with thirst, ravenous hunger, debility, emaciation, transitory hypermetropia, glycosuria and ketonuria. The symptoms abated on dietetic treatment. On admission to the hospital he had considerable glycosuria, ketonuria and hyperglycemia. His diabetes was checked by administration of insulin and has since remained fairly stationary. There has been little tendency to acidosis, but constantly a not inconsiderable glycosuria. Larger doses of insulin might easily lead to hypoglycemia.

In the last couple of years the patient has got increasing pains in the back and left hip, where arthrosis was found to occur. Whereas the pains had formerly subsided for some time after rest in bed and treatment with cod-liver oil and calcium, they have latterly become rather intractable. These pains together with an increasing lassitude and muscular weakness have now made him a man unfit for work and prematurely aged. Otherwise the pigmentation and the findings in the organs were the same as before.

Already before his first admission to the hospital for medical treatment X-ray examination had revealed a severe osteoporosis of the spinal column, with marked decalcification, biconcave deformity of the vertebrae and compression fractures of three vertebrae, corresponding to the kyphosis in the thoraco-lumbar column. The X-rays also showed severe osteoporosis

in the pelvis and in the bones of the thorax. Serum-calcium and serum-phosphorus values were repeatedly found to be normal. A determination of phosphatase also showed normal figures — 3,2 Bodansky units. There was no fatty diarrhea, but gastric achylia was observed.

Of greatest interest is a glucose tolerance test with 65 g of glucose October 1939, a year and a quarter before the symptoms of diabetes made their appearance (Fig. 3). The curve here found is too high and too broad and it shows that a latent diabetes existed already at that time.

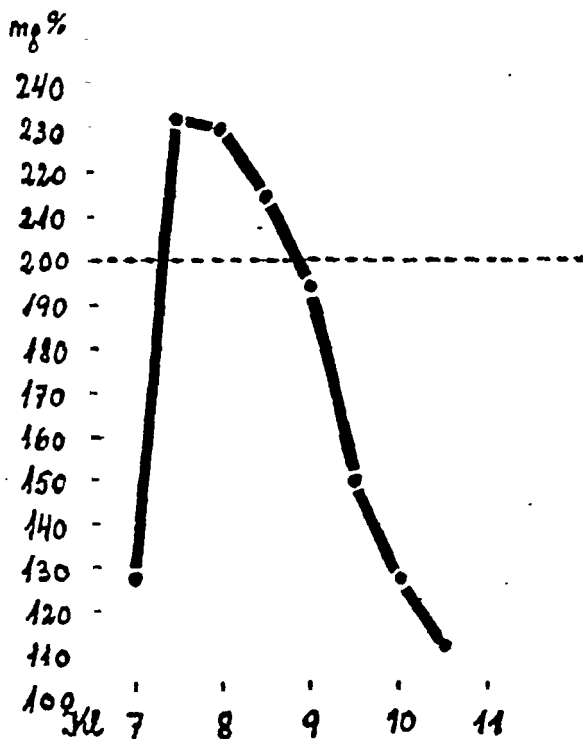


Fig. 3.

Bromsulfalein tests, determination of quinine-resistant lipases in the serum and Takata's test revealed no failure of the liver functions. The prothrombin time was found to be normal. Measurements of adaptation to darkness showed in one instance pathological, but afterwards normal conditions. The icteric index remained normal, from 5 to 7, and there was a moderate degree of urobilinuria.

The behaviour of the blood and blood-forming organs in these conditions has always been regarded with the greatest interest. In our patient normal values were noted for hemoglobin, erythrocytes, reticulocytes and leucocytes. Repeated differential counts revealed a relative lymphocytosis of from 45 to 75 per cent. Sternal puncture showed normal erythropoieses and leucopoiesis. Determination of serum iron in June 1942 revealed

considerable hypersideremia, 241 gamma per cent. During the whole course of the illness there was found an increased sedimentation rate, mostly about 30 mm per hour, at the last examination 65 mm.

As regards other examinations it may be mentioned that Wassermann's and Meinicke's reactions in the blood were negative. Electrocardiograms have shown normal conditions.

Already during his first stay in the hospital the presence of hemochromatosis was suspected on account of the hypertrophic liver and the pigmentations. Meanwhile, a biopsy from the skin revealed only abundant pigment without iron, which, however, is no unusual observation in case of hemochromatosis. As already mentioned, the blood sugar curve also showed that the third main symptom, diabetes, was present, and with the appearance of manifest diabetes the clinical diagnosis was rendered fairly certain. This diagnosis was finally verified by puncture of the liver in March 1941. The histological picture (Fig. 2) shows degeneration of the liver cells and a large increase of the interstitial fibrous tissue. Large quantities of dirty-brown pigment were seen, chiefly as fine granules in the liver cells, but also as coarser masses in the interstitial tissues. The Fontana test for melanin yielded a negative result. On the other hand, an essential part of the pigment gave positive iron-reaction on Turnbull staining.

## II.

*Discussion.* Our two cases are of considerable interest, not only because they present the typical picture of bronzed diabetes, but also because they show features of the disease which have hitherto received little or no attention. The cardiac affection occupies the foremost place in the clinical picture presented by the first patient, while osteoporosis with spontaneous fractures is the most prominent feature in the second case.

Cardiac complications have been observed in many patients with hemochromatosis, but it is believed that these complications are not occasioned by the primary disease. It is true that the myocardium is one of the organs in which hemosiderin is deposited to the largest extent, but signs of degeneration or fibrosis are seldom noted. (1, 2, 3). Electrocardiographic changes have been described in some cases, but it is a remarkable fact that cardiac symptoms have been absent, although autopsies have revealed enormous accumulations of pigment in the myocardium. Meanwhile, when an affection of the coronary vessels with cardiac infarction occurs in so young a man as our first patient, it is reasonable to regard this as having relation to his hemochromatosis.

The presence of a considerable hypercholesterolemia must be viewed in connection with the affection of the coronary vessels and there probably here exists a vascular xanthomatosis of the type described by Carl Müller (4).

As a complication in diabetes Joslin (5) more frequently observes disorders of the coronary vessels in patients with hypercholesterolemia, especially the more permanent form thereof which is not associated with coma or acidosis.

The affection of the coronary vessels may therefore very well be conceived to be a complication of the diabetes. But there is also another possibility, namely, that the existing disturbance in the cholesterol metabolism is due to the liver disease. In uncomplicated portal cirrhosis of the liver blood cholesterol is said to have been found normal or subnormal in most cases, but some cases of hypercholesterolemia have been reported. Weidman and Stokes (6) describe a case of hypertrophic biliary cirrhosis in a child with an exceedingly high blood cholesterol value, classed as a complex xanthoma tuberosum. They state that the rôle of the liver, particularly of hypertrophic cirrhosis, in the development of cutaneous xanthoma has become thoroughly established. Fiessinger and Merklen (7) describe a special variety of hepatic cirrhosis with hypertrophic liver, pigmentation of the skin, hypercholesterolemia and multiple xanthomatosis, but without diabetes. Bech (8) reports a similar case. A causal connection between hepatic cirrhosis, hypercholesterolemia and vascular xanthomatosis is therefore a very obvious possibility.

Osteoporosis in combination with hemochromatosis has earlier been reported by Keith and Mc Nair (9) (one case) and by Sheldon (three cases). In our patient, as well as in the above-mentioned cases, normal values for serum-calcium and serum-phosphorus were found. Likewise the serum-phosphatase was normal in our case. The accumulation of calcium in the organs which was observed by Ramage and Sheldon (1) in cases of hemochromatosis shows that there must have existed unknown disturbances of the calcium metabolism, in spite of the normal conditions in the blood.

In cases of hemochromatosis large quantities of pigment are found in the parathyroid glands (2), in the suprarenals (2, 3) and in the hypophysis (1). Disturbances in the functions of these organs may be supposed to lead to osteoporosis. We have, however, no



criteria for the supposition that the mere accumulation of pigment in the organs has an influence upon their functions.

It is more likely to look upon the osteoporosis as a secondary consequence of the liver disease. Under the designation »osteomalacia hepatica» Ask-Upmark (10) describes a case of severe osteoporosis in liver cirrhosis. A man aged 57, who was suffering from diabetes, got severe osteoporosis. Autopsy revealed hepatic cirrhosis as well as hemochromatosis in liver and pancreas. Ask-Upmark supposes that it is the function of the liver as storage organ for vitamin-D that fails. In our patients hemeralopia was noted as a sign of deficiency in the vitamin- A metabolism.

One point in the history of our second patient deserves attention. Twenty years before the clinical symptoms appeared he was working for two years in a copper mine. In 1920 Mallory, Parker and Nye, on the basis of long-continued injection experiments on rabbits, maintained that chronic copper poisoning may give rise to cirrhosis of the liver and hemochromatosis. Subsequent experimental and clinical investigations, however, have failed to confirm these results. We must therefore assume that it is merely a coincidence that the patient had been working in a copper-mine and we cannot venture to draw any conclusion therefrom as regards a possible causal connection. But even if copper bears no causative relation to hemochromatosis or hepatic cirrhosis, yet the copper metabolism is abnormal in both of these conditions. Herkel (11) showed that in hemochromatosis as well as in cirrhosis of the liver there is generally to be found an accumulation of copper in the organs, especially in the liver, which is seen to have many times more than the normal content of copper. In this connection it would be of interest to have carried out determinations of copper content in the blood serum in these diseases.

### III.

*Pathogenesis:* The pathogenesis of hemochromatosis has been under discussion since the close of the last century and many different views have been advanced. The main interest has now centred firstly on the theory of a disorder of metabolism and secondly on the theory of a hepatic disease as the primary cause.

The existence of a primary metabolic derangement, first and foremost an abnormal iron-metabolism, is maintained by a large

number of authors (Parker 1903, Sprunt 1911, Howard and Stevens 1917, Eldh 1928 and others). In recent years most of those who have devoted attention to the pathogenesis of hemochromatosis have adopted a view similar to that first advanced by Sprunt (2) in 1911, namely, that the primary factor is an intracellular derangement of the iron metabolism, with increased cellular affinity for iron. Sheldon (1), who agrees with this view, bases his conclusion first of all on the fact that his own and earlier investigations seem to show that the blood in hemochromatosis has a low or subnormal content of iron, a circumstance which must be taken as pointing to a retention of iron in the tissues. Sheldon accordingly assumes that determinations of the serum-iron in hemochromatosis would also show low values. The results of serum-iron determinations in our two patients go to show that his assumption is erroneous. Neither have any other convincing arguments been advanced for the theory of a disturbance of intracellular metabolism, nor have we any reliable criteria, either clinical, pathological or experimental, for the assumption that the pigmentation of the organs is the primary element.

The other main theory is to the effect that the hepatic cirrhosis, or, more correctly speaking, a polyscleritis with cirrhosis of liver and pancreas, is the primary factor. The view that the liver disorder is the primary cause was maintained as early as in 1888 by Brault and Galliard. Simmonds (12) was the first to regard the disorder as being a special variety of portal cirrhosis of the liver. Several authors have subsequently adopted this view of hemochromatosis as being the result of an extreme degree of the changes which arise in ordinary liver cirrhosis. The cirrhosis of the liver in hemochromatosis is identical with the usual portal cirrhosis, in which there also occurs a certain degree of hemosiderin pigmentation. In both conditions a chronic interstitial pancreatitis is a feature frequently observed. Barrelet (13) found cirrhosis of the pancreas in half of the cases of liver cirrhosis investigated and in 6 per cent of his cases the pancreatic cirrhosis had manifested itself clinically as diabetes.

In liver cirrhosis there is frequently observed a striking pigmentation of the skin, which becomes brown or dirty-gray. There have been described cases of liver cirrhosis with bronzed pigmentation of the skin, but without hemochromatosis and without diabetes, for

instance, the abovementioned cases (7, 8). In cases of hemochromatosis cirrhosis of the liver is always present. Pigmentation may be lacking; diabetes may be lacking, indeed, it may even be said paradoxically that hemochromatosis may be absent from the picture, but cirrhosis of the liver never fails to appear.

It was likely to suppose that the improved methods employed in recent years for determination in serum of the hemoglobin-free iron fraction should be able to throw new light on these problems. Therefore, in the spring of 1942 determinations of serum-iron were made (by Dr. med. J. Dedichen, University Hospital) in both of our patients by Heilmeyer and Plötner's method (14). The quantity found in patient No. 1 was 225 gamma per cent, later 197 gamma per cent. In patient No. 2 was noted 241 gamma per cent.

The normal values for serum-iron found in adult men by the above method are stated to be the following:

	Min.	Mean	Max.	No. of patients examined
Heilmeyer and Plötner 1937: .....	81 %	126 %	162 %	25
Skouge 1939: .....	79 ,	118 ,	162 ,	50
Sakakura 1940: .....	107 ,	121 ,	135 ,	10
Vahlquist 1941 (statistically computed)	13 ,	142 ,	271 ,	50

In spite of Vahlquist's (15) computation of a very wide range of variation we must assume that the high values found in our patients represent a pathological hypersideremia, far greater than was found in any other of the numerous samples sent in by us for examination.

We have had no opportunity, in the time that has elapsed, to investigate the serum-iron values in portal cirrhosis of the liver. But of greatest interest is the observation reported by Hemmeler (16) that in acute hepatitis there appears with absolute regularity a hypersideremia which develops independently of the bilirubinemia. This observation has been confirmed by Skouge (17) and later by Vahlquist and Waldenström (15). In four cases of cirrhosis hepatis Bjerre and Christoffersen (18) found the following serum-iron values: 165, 171, 149 and 127 gamma per cent. The last was found in a female, the others in males. The highest serum-

iron value found in normal males was 160 gamma per cent. These findings go to show that a cellular disease of the liver may occasion a derangement of the iron metabolism with hypersideremia and that the hypersideremia observed in cases of hemochromatosis is due to the hepatic disorder.

In view of the values found for serum-iron it must be deemed highly probable that hemochromatosis is due to a derangement of metabolism, with increased cellular affinity for iron. In other conditions where there is supposed to exist a special demand for iron in the tissues, particularly in the reticulo-endothelial system in case of acute and chronic diseases due to infection, low serum-iron values are found (15, 17). We should necessarily expect the same to be the case in hemochromatosis, if the tissues there showed increased affinity for iron.

Other causes of hypersideremia in hemochromatosis have not been discerned, no changes in the peripheral blood or in the bone-marrow which could explain the condition, no increased supply of iron, no diminution in the regeneration of red blood corpuscles and no increased destruction of the blood. Neither has there been demonstrated any failure in the functions of the intestine or in those of the kidneys as excretory organs. The liver has long been ascribed an important rôle in the iron metabolism, either as storage organ or as an organ of excretion. There is good reason to suppose that it also in other ways has a regulatory influence on the iron metabolism. We consider it extremely probable that the hypersideremia observed is due to a breakdown in this function of the liver in the iron metabolism. This failure in the liver functions accordingly leads to an increased conveyance of iron with the blood, a process which was previously supposed, but not proved, to take place.

Our conception of the pathogenesis in hemochromatosis may briefly be expressed as follows: Hemochromatosis or bronzed diabetes is due to a primary cirrhosis of the liver and pancreas, in consequence of which there comes a derangement of the iron metabolism with resultant hypersideremia. When the supply of iron is thus increased, the tissues, in which the physical and functional conditions are favourable take up the iron into the cells and deposition of hemosiderin gradually takes place.

In this grave disorder of the liver several other branches of the intermediary metabolism may also be injuriously affected. The

formation of hemofuscin may also very well be explained as a secondary consequence of the liver disease. Retention of sulphur in some of the organs has been observed and the formation of hemofuscin may possibly be connected with a disturbance of the sulphur-protein metabolism. In our cases we have also observed osteoporosis, which was deemed to be due to a disturbance of the calcium metabolism, and hemeralopia ascribed to derangement of the vitamin-A metabolism, while also other circumstances are mentioned which point to a disturbance in the metabolism of cholesterol.

### Summary.

Two cases of hemochromatosis are described. In one of these patients, a man aged 39, the case was complicated by an affection of the coronary vessels with cardiac infarction. The heart trouble is presumed to have been caused by the primary disease. There was noted hypercholesterolemia, which may have been secondary either to his diabetes or to his hepatic disorder. Another complication was hemeralopia. In the other case, a man aged 54, the disease was complicated by severe osteoporosis with spontaneous fractures. It is maintained that this osteoporosis must be deemed to be due to a failure of the liver functions. The patient had worked for two years in a copper-mine, but that fact is not considered to have any etiological significance. The diagnosis was in both cases verified by puncture of the liver. Determinations of serum-iron were made in both cases and hypersideremia was found to be present. It is supposed that this hypersideremia must have been occasioned by the cirrhosis of the liver and, on the other hand, have been the cause of the hemosiderin pigmentation.

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## **Serum phosphatase in thyrotoxicosis and myxoedema.**

By

**POUL BECHGAARD..**

(Submitted for publication February 18, 1943).

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### **Previous Investigations.**

The increase in the basic glycerophosphatase in thyrotoxicosis was observed in 1930 about at the same time by Kay and by Roberts. Among 9 patients with thyrotoxicosis Kay found an increase in phosphatase in 8. He did not enter further into this question. In 1934 Bodansky & Jaffe observed some cases of thyrotoxicosis with increased serum phosphatase and negative calcium balance, and in one case there was at the same time a roentgenographically demonstrable haliteresis. The increases observed were only small, however, and only a few patients were examined in this respect. The negative calcium balance in thyrotoxicosis was first demonstrated by Aub and collaborators and has subsequently been confirmed by other investigators including Robertson.

Later, several authors have taken up the study of this increase in phosphatase from a clinical point of view as well as from an experimental.

By administration of thyroxin, Scoz & Marangoni produced a rise in serum phosphatase in dogs, and in rats they found under the same conditions an increased amount of phosphatase in the

bone. On the other hand, Low, Wilson & Aub were unable to confirm this increase in bone phosphatase. Pelczar & Murza-Murzicz investigated the glycerophosphatase, adenyolphosphatase and guanyolphosphatase in thyroxin-poisoned rabbits. They found a rise of up to 100 %, which on the whole was proportional to the intake of thyroxin, although the animals differed in their individual sensitiveness. After discontinuance of this intoxication the phosphatase values fell off to a normal level. The greatest rise was found for adenyolphosphatase. In patients with exophthalmic goiter the authors found the phosphatase value increased in several cases, but these values were not correlated with the rate of the standard metabolism. Two patients of this kind showed normal values after X-ray treatment. Bowman & Pitts made simultaneous determination of the standard metabolism and the serum phosphatase in a number of cancer patients, without finding any distinct relation between the two values. In one case, for instance, they found rise in the metabolic rate amounting to 50 %, without any coincident increase in phosphatase.

M. Vermehren examined 20 patients with exophthalmic goitre and found in most of them a moderate rise in serum phosphatase, besides an approximate agreement between the degree of the increase in standard metabolism and the rise in phosphatase. Further, in some cases the values obtained varied greatly from one time to another. None of these patients were examined after operation. The highest phosphatase value measured was 288 units. Most of the patients showed values between 85 and 125 units.

Holger Buch found the phosphatase increased in 7 out of 21 patients. There was no demonstrable relation between the rate of the standard metabolism and the phosphatase values but he thought that the cases of longest duration gave the highest values.

### Writer's Investigations.

The purpose of the studies here presented has been to throw some additional light on the course and nature of the increase in serum phosphatase in patients with thyrotoxicosis by following the behavior of this phenomenon in a fairly large number of patients till some point of time after the operation.



### *Patient Material.*

Altogether 83 patients with thyrotoxicosis have been examined, namely, 58 with exophthalmic goiter and 25 with thyrotoxic adenoma. Of these patients, 5 were admitted to the hospital in a state of iodine remission, and the metabolic rate at the beginning of the disease is not known. The material includes all the patients admitted to this department in the period when these studies were going on — with the exception of 2 cases in which the phosphatase determinations failed and 1 case in which tetany developed.

In these 83 cases the amount of serum phosphatase and the rate of standard metabolism were determined twice a week, and the urobilin content of the urine was determined at least once a week. Altogether 11 patients were examined roentgenographically with a view to halisteresis of the vertebral column, namely: some of the most severe cases, some of the most protracted and those with the greatest increase in phosphatase.

62 patients were examined about 10 days after the operation, and 33 of these patients were reexamined 2—6 months after.

A total of about 800 phosphatase determinations were made in these studies.

### **Technique.**

Phosphatase is determined after Lundsten and Vermehren's method, carried out as micromethod on serum.

E. Vermehren states that with this method the normal limits are 17 and 66 units. In 34 persons, in whom there was no reason to expect any increase in phosphatase, the values were found to vary from 29 to 85 units, that is, somewhat higher than the values observed by Vermehren (this difference may possibly be due to the circumstance that at present no glycerophosphate of the same make as was employed by Vermehren has been available). (According to a verbal communication, also Vermehren and others have found a similar increase in the normal phosphatase values on employment of the glycerophosphate used in these studies.)

Accordingly I have reckoned values over 90 units as increased.

Urobilin is determined after Schlesinger's method as modified by Svend Hansen & Marcussen and reckoned pathological in the dilution 1/10 or higher dilution.

The rate of standard metabolism is determined with Krogh's apparatus.

### *Thyrotoxicosis.*

Most of the patients with exophthalmic goitre or thyrotoxic adenoma showed a slight but unquestionable increase in the phosphatase values. Some showed »high normal values»; and a few showed a considerable increase. The distribution of these results is presented graphically in Fig. 1.

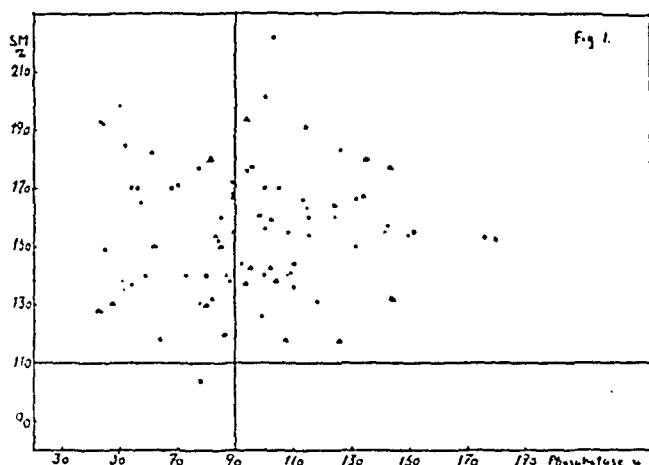


Fig. 1. Relation between the standard metabolism before treatment and average phosphatase values in 50 patients with exophthalmic goiter ( $\blacktriangle$ ) and 24 patients with thyrotoxic adenoma ( $\bullet$ ).

On correlation of these phosphatase values<sup>1</sup> with the metabolic rates prior to the iodine treatment, it is found (Fig. 1) that there is no connection between the increase in phosphatase and the degree of the thyrotoxicosis as expressed by the increasing standard metabolism. This is even more obvious in Fig. 2 in which all the phosphatase determinations and the simultaneous values for the standard metabolism are recorded.

As mentioned, the standard metabolism and phosphatase determinations were made twice a week. Like M. Vermehren, in some cases we found the variations in the values from one time to another to be considerably greater than those seen in normal subjects.

<sup>1</sup> For reasons that will be evident from the following, I have reckoned here with the averages for all the determinations in the preoperative period.

Buch has shown that in a normal subject the serum phosphatase keeps fairly constantly at the same level, and the writer has been able to confirm this finding through frequent determinations from his own blood.

Under the preoperative iodine treatment — in nearly all of these cases with diiodotyrosin — in which the standard metabolism in most instances fell off rather rapidly and considerably, there

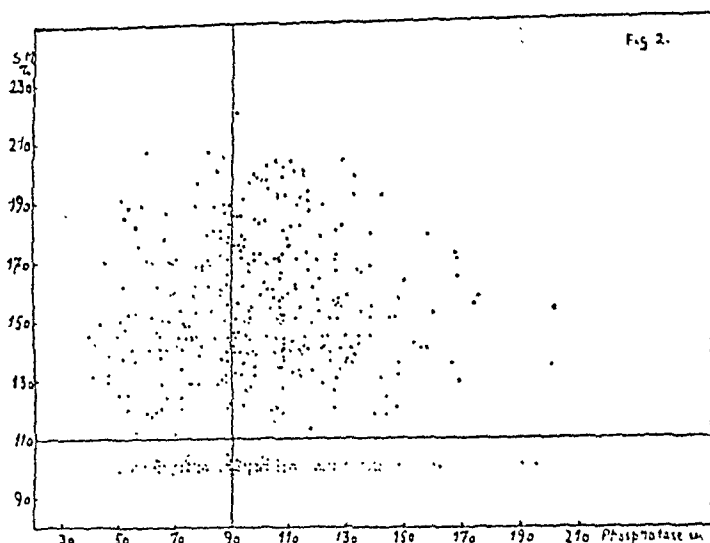


Fig. 2. Relation between serum phosphatase and the simultaneous rate of standard metabolism. The entire material.

appeared no corresponding fall in the phosphatase values, which continued varying round the same level. The variations of the phosphatase values in 4 of these cases are presented graphically in Fig. 3.

In one of these cases the variations from day to day were particularly pronounced. The case record of this patient is in abstract as follows:

*Pt. No. 54/42.* Women, aged 39, married. Admitted to Dep. P. of the Rigshospital 20/2—1/4 and 7/4—9/4—1942. Diagnosis: Exophthalmic goiter.

*Past History.* — No disposition to diseases of the thyroid. Apart from pyuria in 1927 and 1929 and dysuria since, when she catches a cold, she gives a past history of good health.

*Present Illness.* — During the last half year she has had oligomenorrhea, tremor of the hands, palpitation of the heart, sensations of heat, sweating and periodical diarrhea. Enlargement of the thyroid was noticed one month

ago. The appetite has increased, and the patient has not lost in weight. She has not been treated with iodine.

*Physical Examination:* Height: 164 cm. Weight: 53 kg (on admission). Thyrotoxic habitus with motor restlessness. Skin warm and moist. Bilateral exophthalmos. No oedema round the eyes. Joffroy +; Graefe, Kocher & Moebius negative. Slight diffuse enlargement of the thyroid, of soft and homogeneous consistency. No whirring but distinct blowing. Auscultation

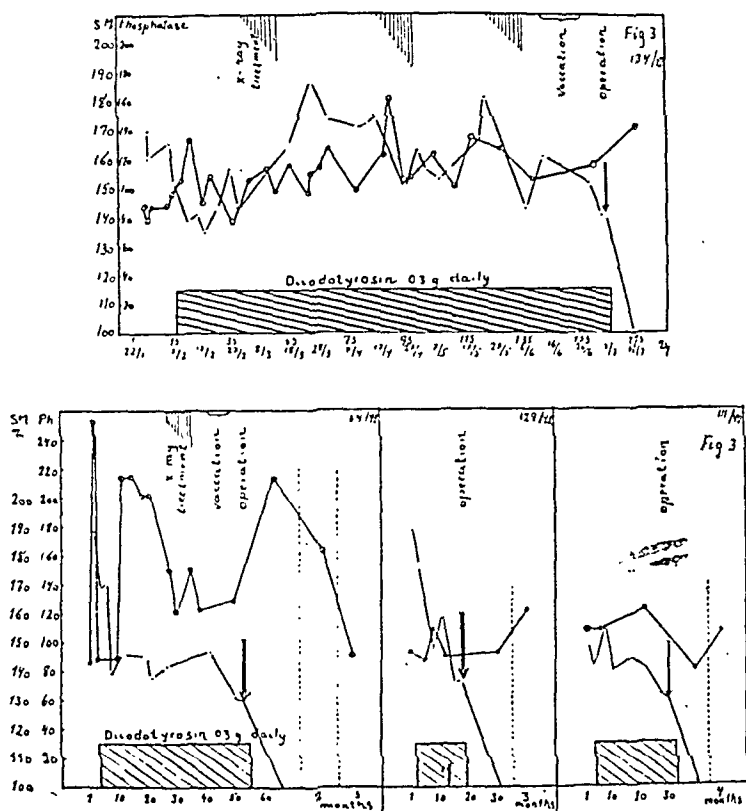


Fig. 3. Serum phosphatase and standard metabolism in 4 cases of thyrotoxicosis.

⊙ — ⊙ = serum phosphatase.  
 ..... = standard metabolism.

of the lungs: Normal findings. Auscultation of the heart: Action regular, 108 beats per min.; otherwise no abnormality. Abdomen normal. Extremities: No abnormality except for a fine rapid tremor of the hands.

Roentgenography: Heart of normal shape and size.

Electrocardiography: Sinus tachycardia; otherwise no abnormality. Blood pressure: 145/85. Urine: No albumin, sugar, blood or pus. Examination for urobilin, thirty times, invariably negative.

Standard metabolism; on admission: 170 % (see Curve). Serum phosphatase: 83 units (see Curve); next day, 252 units.

*Epicrisis:* Case of rather recent origin, which at first reacts slowly to treatment with iodine. Considerable improvement after staying at home in her vacation, after which she is transferred to the surgical department for operative treatment.

Serum phosphatase: After operation, 215 units; 1 ½ months later, 162 units; 5 months later, 90 units.

Reexamination showed no sign of hyper- or hypothyroidism.

Most of the patients were examined again 10—14 days after the operation, when the standard metabolism was normal again. The phosphatase values were still found to keep at the same level

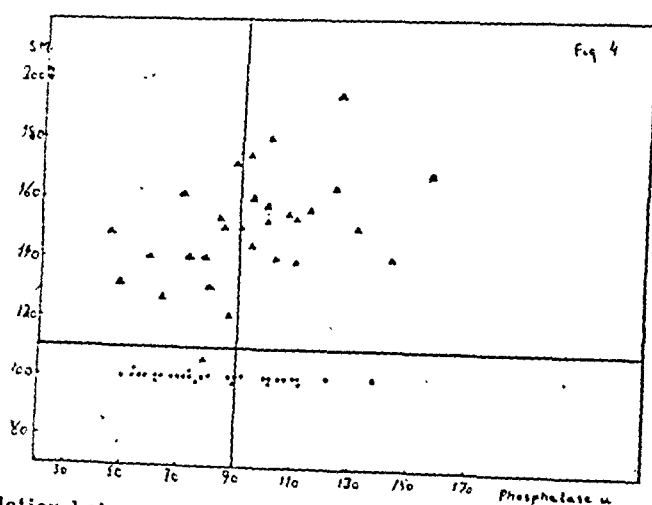


Fig. 4. Relation between serum phosphatase and standard metabolism in the same patients before and 2—6 months after subtotal thyroidectomy.

as prior to the operation, and in some cases even at a higher level (see Figs. 5 and 6).

Of these patients 33 were again examined 2—6 months after the operation. A general clinical examination was performed at the same time as the phosphatase determination, and on patients who were suspect of hyper- or hypothyroidism the rate of standard metabolism was determined.

In these 33 persons who were all found to be well on this examination, the following average values were found for serum phosphatase:

Before the	operation	97.0 units.
Immediately after	»	98.1 »
2—6 months after	»	86.1 »

On the whole, then, there was a fall in serum phosphatase in the course of this period, and in some cases the value had become normal. In some cases, however, the values remained unquestionably increased. For details, see Figs. 4, 5 and 6.

As no definite connection was found between the standard metabolism and the increase in serum phosphatase, it seemed reasonable to investigate whether there might be some difference

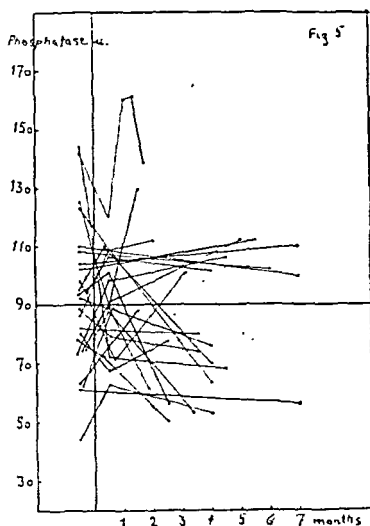


Fig. 5. Phosphatase values just before and 10—14 days after the operation, besides 1—7 months after.

between the phosphatase values in the two forms of thyrotoxicosis in the present material: exophthalmic goiter and thyrotoxic adenoma. As these two lesions differ in various ways as to hereditary aspects, symptoms, duration and age distribution, it was not a priori excluded that they might differ somewhat also with regard to serum phosphatase. The following averages were found for serum phosphatase:

In 83 cases of thyrotoxicosis .....	97.6 units
» 58 » » exophthalmic goiter .....	95.7 »
» 25 » » thyrotoxic adenoma .....	102 »

In thyrotoxic adenoma the average value for serum phosphatase is thus 6.3 units higher than in exophthalmic goiter, but with the wide dispersion of the phosphatase values this difference is not significant. (The standard deviation is respectively  $\pm 9.8$  and  $\pm 8$ .)

Also the possible relation between the duration of the illness and the phosphatase value had to be looked into.

Here only the cases are taken into account in which the duration of illness could be estimated with a fair degree of probability (reckoning the duration of distinct symptoms).

Duration of illness	No. of cases	Serum Maximum	Phosphatase in units Minimum	Average
— ½ year . . . .	18	166	51	89.2
½—1 " . . . .	27	156	45	96.3
1—2 years ..	12	131	59	97.9
2— " . . . .	18	142	47	95.8

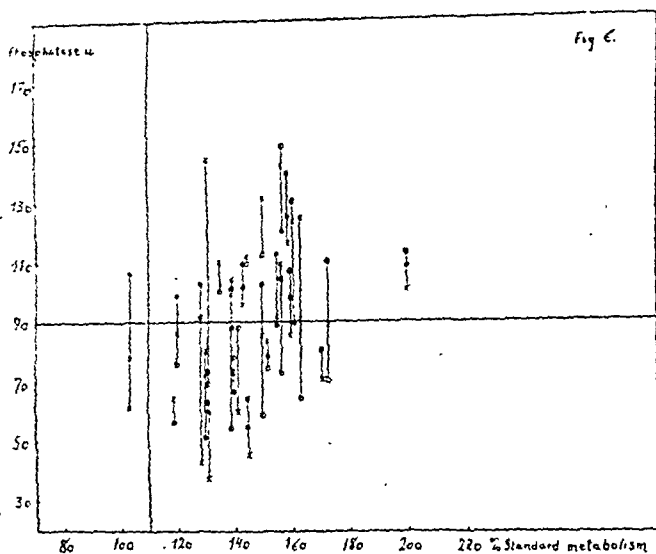


Fig. 6. Relation between the standard metabolism prior to the treatment and the average serum phosphatase before the operation (x), serum phosphatase value just after the operation (•) und 2—6 months after (o)

Thus the average value for cases of less than 6 months' duration is a little lower than the averages for the other groups, but here too the difference is not statistically tenable.

In several patients the thyrotoxicosis is associated with a liver lesion of a somewhat obscure nature, manifesting itself by a periodical appearance of clay-colored stools and by urobilinuria. In 18 cases the presence of urobilin in the urine was demonstrated once or several times. In these cases the average serum phosphatase value was 96.5 units — that is, this affection of the liver gave no additional rise in phosphatase. In the case with the highest

values for serum phosphatase the test for urobilin in the urine, which was performed daily, was constantly negative.

In 11 patients with particularly severe and protracted thyrotoxicosis or particularly high phosphatase values, the lumbar part of the spinal column was roentgenographed with a view to the presence of halisteresis. This abnormality was demonstrated only in one patient — a young man with a severe degree of exophthalmic goiter, in whom the illness had lasted about three years (standard metabolism 190 %) — and here the serum phosphatase was increased (100—125 units).

No calcium balance test was performed.

### *Myxoedema.*

As far as I have been able to find out, the literature has brought no information about serum phosphatase in myxoedema. In view of the antagonism frequently observed between the symptoms in hyper- and hypofunction of the endocrine glands, one might expect to find low, possibly even abnormally low, phosphatase values in myxoedema. As yet I have had no occasion to examine protracted untreated cases of myxoedema.

In 3 of the patients treated operatively for thyrotoxicosis the reexamination revealed a postoperative myxoedema. In these cases the values for serum phosphatase and the standard metabolism were as follows:

	Before operation.		2—6 months after operation.	
	Serum phosphatase	Standard metabolism	Serum phosphatase	Standard metabolism
1. ....	102 units	158 %	66 units	87 %
2. ....	62 "	158 %	60 "	85 %
3. ....	134 "	167 %	110 "	83 %

In 8 patients with myxoedema who had been treated with a thyroid preparation for a considerable length of time and were getting along well on this treatment, the following values were obtained for serum phosphatase and standard metabolism:



	Standard metabolism before treatment	Treatment with thyroid gland	Last standard metabolism	Serum phosphatase
1. ....	?	200 units	103 %	64 units
2. ....	?	1000 "	?	106 "
3. ....	80 %	?	?	76 "
4. ....	?	200 "	100 %	72 "
5. ....	83 %	200 "	?	90 "
6. ....	65 %	400 "	94 %	104 "
7. ....	?	400 "	100 %	84 "
8. ....	84 %	400 "	100 %	72 "

Two of these values for serum phosphatase are decidedly increased; one of these patients was given very large doses of thyroid.

Really low values for serum phosphatase were not found in this patient material; but it has to be admitted that it was not particularly suitable for a decision on this question.

### Discussion.

These studies on serum phosphatase in thyrotoxicosis have confirmed the finding reported by previous investigators: a slight increase in phosphatase in most cases of exophthalmic goiter and thyrotoxic adenoma. On the other hand, these studies have not confirmed the connection which most investigators think they have found between the height of the metabolic rate and the rise in serum phosphatase. Severe and protracted cases of thyrotoxicosis may be associated with normal serum phosphatase, and mild cases with high phosphatase even though, on the whole, the most protracted and severe cases show the greatest rise in serum phosphatase (Fig. 6).

In thyrotoxic adenoma the values for serum phosphatase have on an average been a little higher than in exophthalmic goiter, but the difference is not significant. It would otherwise have been obvious to attribute such a difference to the circumstance that thyrotoxic adenoma develops more insidiously, so that the lesion often persists for a considerable length of time before the patient comes under treatment.

The values for serum phosphatase are not affected by the iodine treatment, nor do they fall off in immediate connection with the operative treatment (subtotal thyroidectomy). It takes several

months after the operation before there is a fall in serum phosphatase, and increased values may still be observed as late as 4—5 months after the operation.

The cause of the rise in serum phosphatase is still obscure. The lack of any relation with the increased standard metabolism makes it rather improbable that the increased serum phosphatase might result from the general accentuation of the cellular function accompanying the thyrotoxicosis. Nor are the phosphatase values particularly high in cases presenting signs of an affection of the liver.

Previous investigators have thought that the rise in serum phosphatase was attributable to the calcium metabolism, and in support of this view they have cited some investigations that show that a negative calcium balance may occur in thyrotoxicosis and also, in a few cases, the phenomenon of halisteresis.

Increase in serum phosphatase is commonly found in several bone lesions and systemic diseases associated with decalcification or new-formation of bone.

Even though halisteresis was found only in one of the present cases, it still seems reasonable to think, that this disturbance in the calcium metabolism — with a slowly progressing decalcification of the bones during the illness and a slow building up of the bones in the convalescence — affords the best explanation of the striking fact that the increase in serum phosphatase is slow in its appearance and persists long after recovery from the illness.

No adequate explanation has yet been found for this disturbance of the calcium metabolism in thyrotoxicosis, and it seems more reasonable, as in other lesions of the calcium metabolism, to look upon the increase in serum phosphatase as a result of the abnormal processes in the osseous system, not as the cause of them.

The practical significance of this increase in serum phosphatase must be said to be slight. For it would be difficult to imagine that it might be of any diagnostic value. Nor has it proved to be of any use for information about the course of the treatment or for an estimation of the prognosis.

In 3 cases of postoperative myxoedema the serum phosphatase values were not particularly low, and the same applies to 8 myxoedematous patients treated with thyroid. No untreated patient with myxoedema of considerable duration has yet been examined.

# Summary.

Altogether 83 patients with thyrotoxicosis — namely, 58 with exophthalmic goiter and 25 with thyrotoxic adenoma have been followed under the preoperative treatment with frequent determinations of serum phosphatase and the standard metabolism, and also for up to 5 months after their operative treatment.

Most of these patients showed a slight increase in serum phosphatase. No connection was found between the increase in standard metabolism and the rise in serum phosphatase. Most often, serum phosphatase kept increased for several months after recovery of the patient from thyrotoxicosis.

The increase in serum phosphatase is thought to be attributable to the calcium metabolism. Similar studies were carried out on 11 patients with myxoedema; they did not show particularly low values for serum phosphatase.

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Die Deutsche Gesellschaft für innere Medizin hält ihre 54. Tagung von Montag, den 11. bis Donnerstag, den 14. Oktober 1943 in Wien unter dem Vorsitz von Herrn Prof. Dr. Eppinger-Wien ab.

Dieselbe ist als Kriegstagung geplant, es kommen dementsprechend vorwiegend nur kriegswichtige Themen zur Besprechung. Bisher sind folgende Vorträge und Referate vorgesehen:

I. Montag, den 11. Oktober 1943 *Kriegsseuchen.*

II. Dienstag, den 12. Oktober 1943

Vormittags: *Feldnephritis.*

Nachmittags: *Infektiöse Erkrankungen des Zentralnervensystems.*

III. Mittwoch, den 13. Oktober 1943

Vormittags: *Hepatitis epidemica.*

Nachmittags: *Freie Vorträge.*

IV. Donnerstag, den 14. Oktober 1943

Vormittags: *Das Ulcus ventriculi und duodeni und seine Behandlung unter dem Gesichtspunkt der Wehreinsatzfähigkeit.*

Die Namen der Referenten werden später bekanntgegeben. Vortragsmeldungen können nur in sehr beschränktem Umfang angenommen werden und sind mit Manuskript bis zum 25. August 1943 an den derzeitigen Vorsitzenden Herrn Professor Dr. Eppinger-Wien, Lazarettgasse 14 I, Medizinische Klinik, zu richten.

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From the Medical Department of the Kommunehospital, Aalborg (Denmark). (Chief: Carl Schwensen, M. D.).

## The Composition of the Blood, and the Blood Pressure in Normal and Hypertonic Persons after Intravenous Injection of Glucose.

By

ALLAN BORBERG, Copenhagen.

(Submitted for publication January 18, 1943).

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The intravenously injected hypertonic glucose solution has been employed experimentally as well as diagnostically and therapeutically, and the composition of the blood after this administration of glucose has been the subject of various investigations. This also holds for the water content of the blood which is the subject of special investigation in this work.

Thus by animal experiments a more or less pronounced temporary hydremia or hydremic plethora was disclosed by v. Brasol, Lipschitz, Albritton, Hanzlik, de Eds and Tainter, Bürger and Bauer, Blalock, Beard, Thuss, and others.

The occurrence of a corresponding hydremia in Man is reported for example by Bürger and Hagemann, Hess, Simenauer, Ellis and Faulkner, whereas Nonnenbruch and Szyzka now find dilution and now concentration of the blood. For all these investigations it holds, however, that a direct determination of the aqueous content of the blood has not been performed, whereas the hydremia has been determined indirectly, for example by the determination of serum protein or serum chlorine, measuring of the viscosity of the blood, of the hemoglobin per cent and cell volume per

cent, or by erythrocyte counting and similar methods, where uncontrollable factors such as changes in the distribution of the blood, mobilisation of unknown depots and the like, may assert themselves. Moreover, a great part of the examined material consists of individuals with disturbances of the water metabolism and edemas, for example persons with cardiac diseases, and (as reported by Simenauer) exsanguine and narcotised patients, all presenting conditions in which a spontaneous dilution of the blood cannot be excluded.

Both dosage and concentration — as well as the speed of injection — have been exceedingly varying but, just as Meyer-Bisch, Marx, Plum and others correspondingly detected a dilution of the blood after peroral administration of glucose, the above-named methods generally disclosed signs of more or less pronounced hydremia after intravenous injection of glucose. The thus observed hydremia is explained by an osmotic action of the glucose, and the authors of a number of other papers agree with this explanation and with the help of more theoretical deliberations come to the same result.

As regards the therapeutic administration of the hypertonic glucose solution, it is now the most commonly employed solution within the so-called osmotherapy. The idea in osmotherapy is the causation of passage of fluid from tissue to the blood by the injection of hypertonic solutions. After such an injection the organism will try to keep up the osmotic balance in the blood, and if there exist abnormal accumulations of some kind of fluid or other, it is assumed that the regulation is effected preferably by their mobilisation. Therefore, this therapy, which constantly is the subject of discussion, has been employed particularly opposite cardiac and circulatory diseases, especially conditions with edemas and acute lung edema, but it has also been used in different other diseases, such as for example hypertonia.

As regards previous investigations in these conditions I refer to Polack and Harpøth's paper in *Hospitalstidende*, 1936. These authors examined the effect produced by intravenous injection of 100 cm<sup>3</sup> of a 50 % glucose solution on the blood pressure in hypertension of different origin and, just as previous authors, they found a decrease of the systolic blood pressure. In the same paper is reported an experiment with a corresponding quantity of glucose admi-

nistered to a patient with normal blood pressure, where the blood pressure likewise tended to decrease. From a blood sugar curve plotted at the same time it is evident that the high values of the blood sugar concentration, which were due to the injection, decreased very rapidly. The urine during the subsequent 24 hours not containing any sugar the following three possible causes of the rapid decrease of the blood sugar were suggested: Combustion, fixation in the carbohydrate depots of the organism or compensation by passage of fluid into the circulation. It is mentioned that, perhaps, all the three factors assert themselves but that the latter factor ought not to be overlooked. Among other authors Hess presumes that the decrease of the blood sugar above all is due to hydremia.

The special scope of the present work is to find out, by direct determination of the water content of the blood, the actual passage of water into the blood stream by intravenous injection of a hypertonic glucose solution, besides a corresponding examination of the conditions in hypertension, one of those pathological conditions which are reported to be influenced favourably by the so-called osmotherapy.

### Methodics.

As glucose preparation was employed sol. glukosi Leo 50 %, and the injection dosage in both series of investigation was 100 cm<sup>3</sup>, i. e. 50 g of glucose, the quantity originally employed in osmotherapy. This was used, partly, because it afforded the possibility of greater reactions in eventual changes of the water content of the blood and, partly, because it made it possible to compare the conditions in the sound with the conditions in the diseased organism.

The fluctuations in the blood sugar caused by the injection were determined at the same time both in venous and capillary blood in order to get an idea of the sugar compensation between blood and tissue. Besides the determinations of the water content of the blood the changes in the cell volume percentage of the blood were examined, and the blood pressure was measured several times. Moreover, the diuresis was measured, and the urine was examined for sugar both qualitatively and quantitatively.



The blood sugar determinations were performed according to Hagedorn and Norman Jensen's method. The samples of venous blood were used immediately after the puncture in order to prevent inaccuracy on account of glycolysis, and the albumin precipitation was carried out as soon as the blood was drawn.

The determinations of the water content of the blood were performed *ad modum* Schwensen. This method briefly consists of drying of the blood in a vacuum exsiccator, and the technic is as follows:

In ordinary weighing-glasses (4 by 5 cm.) is placed a 2 cm. high layer of annealed, granular pimpstone. After drying in the exsiccator on blue gel, the weighing-glasses are weighed and about 0.5 cm<sup>3</sup> of heparin blood is placed in each of them, great care being taken that the fluid strikes the middle of the pimpstone layer. By weighing the glasses again the quantity of blood is ascertained. Now the glasses are placed in the exsiccator, and the air is sucked out until a vacuum of about 20 mm. is reached. Then exsiccation to constant weight was always obtained after 48 hours' standing, that means to say that further exsiccation only yielded variations of less than 1 mg. With the help of these three weighings the water content of the blood is easily calculated. All the weighings were performed with an accuracy of  $\frac{1}{10}$  mg.

The water content of plasma is determined in the same manner after centrifugation of the blood in stoppered glasses.

In order to obtain identical results from duplicate determinations, the following precautions should be used: The distribution of the blood in the weighing-glasses must be effected with the help of a special pipet for each glass. Ordinary eye pipets with rubber caps are practical for this purpose. In consideration of dissimilar sedimentation the pipets on being moved from the blood receptacle to the weighing-glasses should be held in a vertical position. As was demonstrated by Schwensen, it is of importance for the accuracy of the method that the blood is drawn without application of stasis, and that the test person prior to it has been lying flat on his back with his arms straight along the trunk for at least half an hour.

The procedure of drawing the blood was as follows:

With a 5 cm<sup>3</sup> record syringe are drawn about 5 cm<sup>3</sup> of blood from a cubital vein. As stasis is merely used manual compression of the upper arm at the moment the venopuncture is performed. The

blood is at once emptied into a small test-tube containing 0.5—1.0 mg. of heparin Leo G. W. 4.8 and 2 glass beads. The test-tubes are stoppered and turned upside down a couple of times and then stored until later examination. The weighing, however, was always performed immediately after the termination of the experiment, the test-tubes being shaken thoroughly for 1 minute before any blood was removed from them for analysis.

This procedure renders it possible to carry through serial examinations for a longer period without much discomfort for the patients.

The cell volume percentage was determined by centrifugation of the blood in a van Allen hematocrit until the column of blood corpuscles had a constant volume and was lac-coloured in its whole extent. Readings were made with the accuracy of  $\frac{1}{2}$  dividing-line.

The blood pressure was measured with a mercury manometer and the standard technic suggested by English-American authors.

The discharge of sugar in the urine was examined with Almén's solution and Lohnstein's saccharometer.

In all the cases duplicate determinations were performed.

The accuracy of the methods was assayed on 10 samples of blood drawn in immediate succession from the same individual by determining the blood sugar in capillary and venous blood, the water content of total blood and plasma, and the cell volume percentage (hematocrit figures), and the blood pressure was determined by a corresponding number of measurings.

The mean error on the mean value of duplicate determinations was calculated to be:

Blood sugar (capillary blood): .....	$\pm 0.005 \%$
Blood sugar (venous blood).....	$\pm 0.006 \%$
Water content of total blood: .....	$\pm 0.083 \%$
Water content of plasma: .....	$\pm 0.087 \%$
Hematocrit figure: .....	$\pm 0.36 \%$
Blood pressure (systolic): .....	$\pm 2.2 \text{ mm.}$

The limits of error are easily calculated by multiplying these figures by 3.

As the analyses of the blood samples with regard to the content of water could not be performed till the termination of the experiment, it was examined whether a change in the water content would

take place in heparin blood which was allowed to stand for 4 hours, the detected variations proved to be far within the limits of error.

Thus the experiments were performed in the following manner.

The test person having received ordinary ward diet for several days, must abstain from food during the last 14 hours prior to the experiment, nor is he allowed to drink anything during that time in order to prevent errors in the resorption of fluid from the intestine. Then, immediately after micturition, he is requested to lie down quietly for 1 hour with his arms straight along the trunk. The cuff of the sphygmometer is placed on the left upper arm, and the tension is measured 3 times during that hour, the lowest value found being used as starting value. After the lapse of an hour 5 cm<sup>3</sup> of blood are drawn from the other arm by venopuncture without stasis and emptied into a test-tube containing 0.5—1.0 mg. of heparin. From this tube a sample is taken for the examination of the fasting blood sugar and cell volume percentage; then the tube is stoppered and stored for later examination. A sample of blood is also drawn from the ear for determinations of blood sugar and hemoglobin. Subsequently 100 cm<sup>3</sup> of a 50 % glucose solution were injected intravenously in the left arm in the course of 2—3 minutes. Within from 1 to 5 minutes after the injection venopuncture was made on the right arm with withdrawal of about 5 cm<sup>3</sup> of blood, a sample of which was used for determining the blood sugar and cell volume percentage. Moreover, at the highest 1 minute after the puncture a sample of blood was drawn from the ear for determining the blood sugar.

These examinations were repeated during the next 3 hours, namely, 10, 25, 40, 60, 90, 120, 150, and 180 minutes after the injection of glucose. The blood pressure was measured as soon as possible after the withdrawal of the blood samples, and it was moreover controlled 3 and 24 hours after the termination of the experiment. The diuresis from the subsequent 20 hours was measured and examined for sugar, the first portion of urine passed immediately after the termination of the experiment being examined separately.

Besides these examinations, determinations of the hemoglobin percentage (Zeiss' hemometer) in capillary blood were performed in isolated cases at the same time as the blood sugar determinations during the first hour after the injection.

### Examinations of normal individuals.

The material of normal persons consisted of 8 apprentice hospital nurses, aged 23—31 years, who were kind enough to submit to the examination of these conditions. They felt and looked all well, and had been submitted to medical examination before they were engaged, whence it is warrantable to regard them as being healthy.

L., ♀, æt. 23 years. Weight 68 kg. Hb. 90 %. Urine without ABPS.  
Blood pressure: 125/85, 125/85, 125/85.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	475	297	216	179	125	107	90	90	80
vein .....	90	439	256	179	143	90	90	81	72	72
Water content in total blood ..	80.25	82.26	81.41	80.57	80.15	79.88	80.06	79.94	80.11	79.68
plasma .....	90.60	92.65	91.90	90.85	90.34	90.01	90.52	90.08	90.59	89.80
Cell volume % ..	39	35	37	40	40.5	39	40	40	40.5	40.5
Blood pressure ....	125/85	120/85	115/85	115/	115/	120/85	120/	120/	120/85	

Blood pressure after 3 and after 24 hours: 125/85

Urine immediately after examination: 500 cm<sup>3</sup>, Lohmstein 1.3 % = 6.5 g. of glucose.

Urine from the subsequent 20 hours: 800 cm<sup>3</sup>, without sugar.

M. N., ♀, æt. 28 years. Weight 64 kg. Hb 92 %. Urine without ABPS.  
Blood pressure: 130/80, 130/80, 130/80.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	495	403	244	197	143	116	99	90	81
vein .....	90	457	370	224	188	134	108	90	90	72
Water content in total blood ..	80.40	82.62	82.03	81.27	80.86	80.74	80.59	80.26	80.34	80.66
plasma .....	90.52	92.77	92.35	91.62	91.08	90.94	90.84	90.40	90.52	90.72
Cell volume % ....	36.5	32.5	34	34.5	36	37	36	36.5	36.5	36.5
Blood pressure ....	130/80	130/80	120/80	120/	120/	120/	120/	120/	130/80	130/80

Blood pressure after 3 and after 24 hours: 130/80

Urine immediately after examination: 550 cm<sup>3</sup>, Lohmstein 1.9 % = 10.45 g. of glucose.

Urine from the subsequent 20 hours: 500 cm<sup>3</sup>, Lohmstein 0.3 % = 1.5 g. of glucose.

K. M., ♀, æt. 24 years. Weight 56 kg. Hb. 90 %. Urine without ABPS.  
Blood pressure 110/75, 110/75, 110/75.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	72	484	390	232	188	152	116	90	90	79
vein .....	72	448	365	214	175	134	99	81	72	63
Water content in total blood ..	80.29	81.77	81.05	80.51	79.94	80.10	79.89	79.52	79.32	79.22
plasma .....	90.64	92.09	91.42	90.92	90.45	90.52	90.32	90.14	90.18	90.08
Cell volume % ....	39	35	35	36	37	37.5	37.5	38	39	40.5
Blood pressure ....	110/75	110/75	105/75	105/	105/	110/75	110/	110/	110/	110/75

Blood pressure after 3 and after 24 hours: 110/75

Urine immediately after examination: 650 cm<sup>3</sup>, Lohnstein 1 % = 6.5 g. of glucose.

Urine from the subsequent 20 hours: 700 cm<sup>3</sup>, Lohnstein 0.2 % = 1.4 g. of glucose.

S. M., ♀ æt. 26 years. Weight 64 kg. Hb. 107 %. Urine without ABPS.  
Blood pressure: 110/80, 110/80, 110/80.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	81	480	306	226	188	150	104	90	80	90
vein .....	81	442	272	206	170	127	99	82	72	84
Water content in total blood ..	79.71	81.73	80.54	79.62	79.26	79.06	78.95	79.00	79.00	79.23
plasma .....	90.15	92.06	90.88	90.20	89.84	89.70	89.48	89.56	89.68	89.96
Cell volume % ....	40	37.5	39	40	40	41	41	41	41.5	41.5
Blood pressure ....	110/80	105/80	105/	105/	105/	105/	110/80	110/	110/80	110/80

Blood pressure after 3 and after 24 hours: 110/80

Urine immediately after examination: 800 cm<sup>3</sup>, Lohnstein 0.6 % = 4.8 g. of glucose.

Urine from the subsequent 20 hours: 725 cm<sup>3</sup>, without sugar.

For safety's sake the urine was examined and the hemoglobin percentage was determined prior to the experiments. None of the girls was menstruated at the time of examination.

The results derived from the above-described examinations of these test persons are recorded in the schemes.

E. M., ♀, æt. 24 years. Weight 59 kg. Hb. 90 %. Urine without ABPS.  
Blood pressure 105/70, 105/70, 105/70.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	466	385	216	152	116	99	81	81	81
vein .....	90	430	358	188	140	110	90	81	72	72
Water content in total blood ..	80.15	82.01	81.20	80.68	80.73	80.44	80.32	80.05	79.66	79.96
plasma .....	90.52	92.46	91.67	91.12	91.20	91.08	90.98	90.68	90.26	90.44
Cell volume % ....	36	34	34.5	35.5	36	35	36	37	37.5	37.5
Blood pressure ....	105/70	115/70	100/70	95/70	100/	100/	100/	100/	100/	100/70

Blood pressure after 3 and after 24 hours: 105/70

Urine immediately after examination: 400 cm<sup>3</sup>, Lohnstein 2 % = 8 g. of glucose.

Urine from the subsequent 20 hours: 650 cm<sup>3</sup>, without sugar.

K., ♀, æt. 25 years. Weight 64 kg. Hb. 102 %. Urine without ABPS.  
Blood pressure: 125/80, 120/80, 120/80.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	70	396	347	234	198	114	95	75	72	80
vein .....	70	370	310	216	161	110	79	75	72	75
Water content in total blood ..	78.94	80.57	80.04	79.52	79.23	79.12	78.88	79.24	79.39	79.31
plasma .....	90.61	92.38	91.68	91.20	91.02	90.92	90.60	90.99	91.02	91.08
Cell volume % ....	43	40	40	41	41.5	41.5	42.5	42	43	43
Blood pressure ....	120/80	130/80	120/80	115/80	120/	120/	120/	120/	120/	120/80

Blood pressure after 3 and after 24 hours: 120/80

Urine immediately after examination: 600 cm<sup>3</sup>, Lohnstein 0.7 % = 4.2 g. of glucose.

Urine from the subsequent 20 hours: 500 cm<sup>3</sup>, Lohnstein 0.2 % = 1 g. of glucose.

### Discussion of the conditions in the normal.

Congestions, which are of common occurrence after intravenous injections, were observed in all the cases but they disappeared rapidly again. Complications were not observed in any of the test persons, but in view of the possibility of such the injections were made in the left arm. Nor do Polack and Harpøth report ever

P., ♀, æt. 31 years. Weight 76 kg. (Height 172 cm). Hb. 100 %. Urine without ABPS.

Blood pressure: 125/80, 125/80, 125/80.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	88	403	315	220	175	108	90	81	72	72
vein .....	92	370	284	197	162	90	90	72	72	64
Water content in total blood ..	79.94	80.94	80.27	79.96	79.46	79.46	79.72	79.89	80.16	80.22
plasma .....	90.84	91.88	91.25	91.01	90.50	90.65	90.74	90.72	90.80	90.88
Cell volume % ....	39	36.5	37.5	37.5	38	39	38	39.5	39	39
Blood pressure ....	125/80	130/80	120/80	120/	120/	120/	125/80	125/	125/80	
Hb. % .....	100	81	84	89	93	95				

Blood pressure after 3 and after 24 hours: 125/80

Urine immediately after examination: 600 cm<sup>3</sup>, Lohnstein 1.5 % = 9 g. of glucose.

Urine from the subsequent 20 hours: 600 cm<sup>3</sup>, without sugar.

J., ♀, æt. 31 years. Weight 50 kg. Hb. 100 %. Urine without ABPS.

Blood pressure: 120/75, 120/75, 115/75.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	593	443	331	225	145	125	102	90	90
vein .....	90	490	415	305	193	127	106	90	94	80
Water content in total blood ..	79.72	81.31	80.36	80.10	79.47	79.08	79.32	79.31	79.60	79.98
plasma .....	90.57	92.10	91.19	90.81	90.23	90.04	90.25	90.40	90.62	90.64
Cell volume % ....	44	39	40	39.5	43	43	44.5	44	44	44
Blood pressure ....	115/75	125/75	105/75	110/75	110/	110/	115/75	115/	115/75	
Hb. % .....	100	86	89	89	98	98				

Blood pressure after 3 and after 24 hours: 115/75

Urine immediately after examination: 450 cm<sup>3</sup>, Lohnstein 2.4 % = 10.8 g. of glucose.

Urine from the subsequent 20 hours: 500 cm<sup>3</sup>, without sugar.

having met with complications, but apart from discomforts after paravenous injection, they are by Tunbridge and Allibone reported to occur sometimes in the form of headache, cold shiver, rise of temperature and, in isolated cases, of aseptic phlebitis. However, such complications seem to occur only in cases, where preparations are used which are not quite pure.

The experimental material consisting of young women in a medium state of nutrition, the injected quantity of glucose will on the whole correspond to a fairly uniform dosage. Dosage according to weight was not used, because it usually is not employed in osmotherapy.

Since there are but few reports of repeated determinations of the sugar content of capillary and venous blood after intravenous injection of glucose, the conditions of the blood sugar will be described a little more in detail.

As regards the initial increase of blood sugar it is not so considerable as might be anticipated after the quantity injected, but it concords with the fact demonstrated by Jørgensen and others that there is no proportionality between the quantity of glucose injected and the increase of blood sugar obtained. As was emphasized for example by Pavy, the rate of injection is of importance for the absolute increase of the percentage of blood sugar. Investigations by Jørgensen and Plum have shown that the maximal value is reached immediately after the injection, and that it is followed at once by a sharp and continuous incline of the curve.

The very rapid disappearance of the sugar from the blood, which according to Jørgensen begins already during the injection, is assumed to be due primarily to a purely physical distribution of the sugar between blood and tissue fluid in connection with deposition and combustion of the glucose. Bergmark, Bernstein and Falta after intravenous glucose injection found an increase of the respiratory quotient; however, in perfect rest the organism cannot be assumed to consume the relatively great quantities of glucose just as rapidly as they are removed from the blood, particularly as the glucose has been introduced into the organism outside of the liver, which is the chief seat of the carbohydrate metabolism. Norn's investigations in metabolism show, moreover, that the major quantity of perorally administered glucose is deposited in the course of the first couple of hours, only a fraction being consumed.

This removal of glucose from the blood takes place so rapidly, however, that the rise and shape of the blood sugar curve after the liberal dose here employed does not differ essentially from that of the normal glucose curve after introduction of much less glucose. Thus Jørgensen after intravenous injection of 20 g. of glucose



with a rate of injection of from 3 to 4 minutes found an increase of up to 400 mg. % and return to fasting values in the course of 90 minutes. That corresponds to what K. M. Hansen found, namely, that the organism with increasing blood sugar concentration seems to acquire an increasing power of removing the sugar from the blood. The variations in the initial increase, which was observed in the present work, besides to minor fluctuations in the injection time may be attributed to several factors, for example the different magnitude of the quantity of blood and, probably, also the different repletion of the carbohydrate depots of the organism, which according to Stenström's investigations is at any rate of importance in case of peroral application of glucose.

Hagedorn is the first who demonstrated that, whereas the same glucose concentration in capillary and venous blood was found during fasting, the capillary blood of the normal after administration of carbohydrate has a higher glucose level than has venous blood. This is particularly pronounced in case of high blood sugar level, being the expression of greater absorption of sugar in the tissues. Rosenow examined the difference of the blood sugar level between arterial and venous blood after intravenous injection of 20 cm<sup>3</sup> of a 50 % glucose solution, and averagely found a difference of from 26 to 36 mg. % as well as a parallelism between the arterial and venous sugar curves, which he regards as an expression of the rapid compensation between blood and tissues.

This difference between capillary and venous blood sugar was also detected in the present investigations, and it amounted to 35 mg. % on an average, in isolated cases up to 49 mg. %, immediately after the injection. During the decrease of the blood sugar the two curves become more uniform, the difference finally lying within the limits of error, but it is evident that, at any rate in the higher concentrations of the blood sugar, a considerable and rapid elimination of sugar from the blood takes place during the perfusion through the tissues.

As a termination of the blood sugar decrease is frequently observed — as was also reported by numerous authors — a post-hyperglycemic hypoglycemia which is explained by an excessive insulin production, and one of the reasons why the examinations were carried on for 3 hours was my desire to detect eventual fluctuations in the water content of the blood during that phase.

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As a termination of the blood sugar decrease is frequently observed — as was also reported by numerous authors — a post-hyperglycemic hypoglycemia which is explained by an excessive insulin production, and one of the reasons why the examinations were carried on for 3 hours was my desire to detect eventual fluctuations in the water content of the blood during that phase.

about 1 per cent above the fasting values. The reason why this great dose of glucose apparently does not give rise to any distinct hydremia exceeding that which can be explained by the injected water, probably and above all is the compensation of sugar between blood and tissue taking place so rapidly that the osmotic effect only becomes very brief. Moreover, the increased water content of the blood probably is excreted rapidly through the kidneys by the increased diuresis, just as part of it during the deposition of the glucose is bound to the tissues. Pfeiffer reports for example that intravenous injection of glucose gives rise to temporary fixation of water in the liver. It is a wellknown fact that there is a close relationship between carbohydrate metabolism and water metabolism, and it is possible that the increased excretion of insulin due to the glucose injection is of importance. Thus Winter demonstrated a decrease of the water content of the blood after subcutaneous injection of insulin.

The minor increase in the water content of the blood observed in some cases in subsequently drawn samples is, perhaps, due to liberation of this water during the gradual combustion of the glucose. In some cases the blood concentration at the termination of the experiment, i. e. during the hypoglycemic phase, seems also to be somewhat higher than the fasting values, and that may be due to slight dehydration of the blood on account of the increased diuresis. These fluctuations are, however, too small to permit of inferring anything from them.

It is possible that the glucose under pathological conditions such as for example edematous conditions, when the passage through the capillary wall is, perhaps, difficult, may give rise to absorption of water in the blood, but under normal conditions such an absorption apparently does not take place in a detectable degree.

Together with the increase in the water content of the blood, the cell volume per cent of the blood decreased, although but little, i. e. about 3 volume per cent on an average, and the hematocrit number fairly rapidly returned to the initial values. According to Engghoff's investigations the addition of heparin is without importance for the determination of the cell volume per cent of the blood.

The blood pressure showed but slight fluctuations. In the majority of cases a minor decrease (from 5 to 10 mm.) of the systolic blood pressure was noted immediately after the injection. In some

### Examinations of Hypertonics.

The hypertension material consists of 8 patients with essential or secondary hypertension of different gravity. These patients were submitted to examinations of blood pressure repeated at days' intervals, and electrocardiography as well as different examinations

Casebook No. 1277/42, L., ♂, aet. 21 years. Essential juvenile arterial hypertension. Weight 66 kg. Hb. 113 %. Metabolism 92 %. Urine without ABPS. Microscopy negative. Urography normal. Maximal clearance 78. Blood pressure: 170/110, 170/110, 170/110.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	546	473	348	266	179	143	107	90	72
vein .....	90	502	441	321	236	170	125	90	81	72
Water content in total blood ..	77.34	79.00	78.01	77.77	77.71	77.68	77.29	77.07	76.90	77.02
plasma .....	89.73	91.50	90.87	90.59	90.45	90.31	89.96	89.88	89.90	89.70
Cell volume % ....	49	44.5	45.5	46	47	48.5	48	47.5	47	49.5
Blood pressure ....	170/110	160/110	140/100	140/	140/	140/	140/	140/	140/	140/100

Blood pressure after 3 and after 24 hours: 170/110

Urine immediately after examination: 300 cm<sup>3</sup>, Lohnstein 3% = 9 g. of glucose.

Urine from the subsequent 20 hours: 850 cm<sup>3</sup>, without sugar.

Casebook No. 1340/42, S., ♀, aet. 58 years. Essential arterial hypertension, chronic progressive primary polyarthritis. Weight 73 kg. Hb. 96 %. Urine without ABPS. Microscopy negative. Strauss' test: Diuresis 2200 cm<sup>3</sup>, specific gravity 1.001/1.028. Blood pressure: 205/115, 205/115, 205/115.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	467	428	339	284	244	188	143	125	101
vein .....	90	439	403	315	254	233	176	140	110	90
Water content in total blood ..	80.31	81.85	81.09	80.58	80.70	80.60	80.27	80.73	81.05	80.71
plasma .....	90.05	91.53	90.90	90.51	90.88	90.86	90.25	90.72	91.12	90.69
Cell volume % ....	35.5	32	33.5	34.5	34	34	35	34	34	34.5
Blood pressure ....	205/115	190/110	180/110	180/	180/	180/	180/	180/	180/	180/110

Blood pressure after 3 hours: 185/110

Blood pressure after 24 hours: 205/115

Urine immediately after examination: 950 cm<sup>3</sup>, Lohnstein 1 % = 9.5 g. of glucose.

Urine from the subsequent 20 hours: 450 cm<sup>3</sup>, without sugar.

Casebook No. 1264/42. J., ♂, æt. 36 years. Arterial hypertension, chronic nephritis, syphilis, anemia. Weight 82 kg. Hb. 69 %. Urine: + albumin, + blood, no sugar, no pus. Microscopy: ++ erythrocytes, + cylinders. Strauss' test: Diuresis 2100 cm<sup>3</sup>, specific gravity 1.002/1.024. Maximal clearance 20. Blood pressure: 190/120, 190/120, 190/120.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	451	306	266	209	153	125	72	60	45
vein .....	90	421	276	240	198	143	107	88	54	54
Water content in total blood ..	82.06	83.96	82.76	82.28	82.16	82.27	82.21	81.95	82.08	82.14
plasma .....	89.88	91.84	90.56	90.26	90.09	90.11	90.23	89.80	90.00	90.04
Cell volume % ....	28.5	25.5	26	27.5	27	28	27	27.5	27.5	28
Blood pressure ....	190/120	200/120	180/110	180/	180/	180/	190/120	190/	190/120	

\* Blood pressure after 3 and after 24 hours: 190/120  
 Urine immediately after examination: 500 cm<sup>3</sup>, Lohnstein 0.6 % = 3 g. of glucose.  
 Urine from the subsequent 20 hours: 500 cm<sup>3</sup>, without sugar.

Casebook No. 1396/42. M., ♀, æt. 71 years. Arterial hypertension, nephrosclerosis. Weight 67 kg. Hb. 120 %. Urine: + albumin, no blood, sugar or pus. Microscopy negative. Strauss' test: Diuresis 1250 cm<sup>3</sup>, specific gravity 1.001/1.015. Blood pressure: 190/110, 190/110, 190/110.

	Fasting values	Minutes after injection								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	488	410	263	226	199	150	118	89	68
vein .....	90	448	379	238	216	182	137	100	89	68
Water content in total blood ..	74.43	76.00	75.86	75.05	74.95	74.87	74.75	74.72	74.31	74.02
plasma .....	90.48	91.98	91.79	91.12	90.86	90.71	90.65	90.56	90.42	90.25
Cell volume % ....	56.5	51	51	52.5	53.5	54.5	55	55.5	56	56
Blood pressure ....	190/110	195/110	160/105	160/	170/105	170/	180/105	180	185/110	

Blood pressure after 3 and after 24 hours: 190/110  
 Urine immediately after examination: 130 cm<sup>3</sup>, Lohnstein 2.4 % = 3.12 g. of glucose.  
 Urine from the subsequent 20 hours: 250 cm<sup>3</sup>, without sugar.

with regard to kidney disease, namely, chemical and microscopical examinations of the urine, determination of urea, Strauss' kidney function test and, eventually, urea clearance test. Moreover, ophthalmoscopical (specialist) and neurological examinations were performed in all the cases, besides, in a couple of cases, determinations of metabolism in order to be able to diagnose essential hyper-

Casebook No. 1920/42. A, ♂, æt. 37 years. Arterial hypertension, hyperthyroidism. Weight 69 kg. Hb. 111 %. Metabolism 146—143 %. Urine without ABPS. Microscopy negative. Standard clearance 52. Blood pressure: 190/105, 190/105, 190/105.

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	70	421	297	256	220	198	169	134	98	90
vein .....	70	385	276	236	210	179	151	125	102	90
Water content in total blood ..	77.53	79.11	78.72	78.32	78.02	77.99	77.75	77.33	77.67	78.19
plasma .....	91.06	92.51	92.02	91.75	91.29	91.28	91.15	90.84	91.03	91.34
Cell volume % ....	49	44	45	46	46.5	47	46	46	47	48
Blood pressure ....	190/105	190/105	165/95	165/	170/100	170/	180/105	185/105	185/105	185/105

Blood pressure after 3 hours: 185/105

Blood pressure after 24 hours: 190/105

Urine immediately after examination: 280 cm<sup>3</sup>, Lohnstein 0.9 % = 2.52 g. of glucose.

Urine from the subsequent 20 hours: 825 cm<sup>3</sup>, without sugar.

Casebook No. 1518/42. C., ♀, æt. 55 years. Arterial hypertension, myxedema. Weight 81.5 kg. Hb. 93 %. Urine without ABPS. Microscopy negative. Metabolism 82—73 %. Strauss' test: Diuresis 2600 cm<sup>3</sup>, specific gravity 1.001/1.026. Blood pressure: 190/120, 190/120, 190/120

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	72	448	403	320	264	225	188	161	125	90
vein .....	72	429	386	294	245	215	179	148	110	90
Water content in total blood ..	79.76	81.28	80.66	80.30	80.26	79.95	79.90	79.69	79.51	79.66
plasma .....	88.20	89.72	89.12	88.81	88.50	88.31	88.18	88.15	88.20	88.25
Cell volume % ....	36	32	33	33.5	34	34	35	35	35	35
Blood pressure ....	190/120	185/120	170/110	165/110	165/	165/	165/	165/	165/	165/110
Hb. % .....	93	84	84	85	89	90				

Blood pressure after 3 hours: 165/110

Blood pressure after 24 hours: 190/120

Urine immediately after examination: 320 cm<sup>3</sup>, Lohnstein 0.5 % = 1.6 g. of glucose.

Urine from the subsequent 20 hours: 1000 cm<sup>3</sup>, without sugar.

tension with the greatest possible certainty. In none of these patients was the hypertonic condition complicated by pronounced adipositas, diabetes mellitus, glycosuria, uncompensated cardiac insufficiency or manifest edema.

Casebook No. 1375/42. H., ♀, æt. 70 years. Arterial hypertension, arteriosclerosis, bronchitis. Weight 81 kg. Hb. 95 %. Urine without ABPS. Microscopy negative. Strauss' test: Diuresis 1500 cm<sup>3</sup>, specific gravity 1.001/1.030. Blood pressure: 190/100, 190/100, 190/100 (pronounced peripheral arteriosclerosis).

	Fasting values	Minutes after injection								
		4	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	80	439	390	309	276	236	188	143	107	90
vein .....	80	420	361	297	256	217	179	143	107	85
Water content in total blood ..	80.21	82.24	81.77	81.20	80.66	80.80	80.26	80.32	79.90	79.92
plasma .....	89.75	91.72	91.50	90.88	90.30	90.45	89.90	89.97	89.63	89.72
Cell volume % ....	38.5	35	35	37	38	36.5	39	38.5	38.5	39
Blood pressure ....	190/100	180/100	180/	185/100	185/	190/100	190/	190/	190/	190/100

Blood pressure after 3 and after 24 hours: 190/100

Urine immediately after examination: 250 cm<sup>3</sup>, Lohnstein 1 % = 2.5 g. of glucose.

Urine from the subsequent 20 hours: 500 cm<sup>3</sup>, Lohnstein 0.2 % = 1 g. of glucose.

Casebook No. 1005/42. A., ♂, æt. 53 years. Arterial hypertension, arteriosclerosis, myocardial degeneration. Weight 63 kg. Hb. 99 %. Urine without ABPS. Microscopy negative. Strauss' test: Diuresis 1300 cm<sup>3</sup>, specific gravity 1.001/1.028. Blood pressure: 185/130, 185/130, 185/130. (pronounced peripheral as well as retinal arteriosclerosis).

	Fasting values	Minutes after injection.								
		½	10	25	40	60	90	120	150	180
Blood sugar in capillary ....	90	475	403	298	254	225	197	161	125	90
vein .....	90	457	375	274	235	216	179	160	115	81
Water content in total blood ..	79.49	81.72	80.43	79.85	79.45	79.12	79.36	79.34	78.89	79.10
plasma .....	90.53	92.61	91.42	90.89	90.62	90.30	90.57	90.63	90.24	90.32
Cell volume % ....	42	37.5	38	41	42	44	43	42	42.5	42
Blood pressure ....	185/130	190/130	185/130	185/	185/	185/	185/	185/	185/	185/130
Hb. % .....	99	90	95	96	96	96				

Blood pressure after 3 and after 24 hours: 185/130

Urine immediately after examination: 375 cm<sup>3</sup>, Lohnstein 1.5 % = 5.6 g. of glucose.

Urine from the subsequent 20 hours: 110 cm<sup>3</sup>, without sugar.

Moreover, all the patients had been confined to bed for 8 days before the experiments were carried out, Strauss' test being performed subsequent to them in order to prevent a possible error in the quantity of water administered.

The examinations of the 8 patients thus revealed the following forms of hypertonia:

Essential hypertension .....	2 cases
Hypertension + kidney disease .....	2 »
Hypertension + metabolic disturbance .....	2 »
Hypertension + arteriosclerosis .....	2 »

### Discussion of the Conditions in Hypertonics.

From the results of the experiments it is evident that the conditions, particularly the fluctuations in the water content of the blood, of these hypertonics do not differ essentially from those of the normal. Nor did these examinations apart from the congestions disclose any discomforts or complications in connection with the injections. On the other hand the patients did not feel better after them.

Supposing the limit to be 110 mg. %, the fasting blood sugar was found to be normal and identical in capillary and venous blood. By way of comparison it may be mentioned that Brems finds normal fasting blood sugar in hypertonics without manifest kidney disease, whereas Hetényi reports to have found hyperglycemia in nearly all forms of hypertension. Kylin reports that there is a distinct tendency to hyperglycemic fasting values in essential hypertension, and Dörle and Frank find higher fasting values in venous than in capillary blood of hypertonics. As regards the increase of the blood sugar subsequent to the injection, it does not differ from corresponding findings in the normal. On the other hand, the shape of the blood sugar curve in 5 of the cases (No. 1340, 1920, 1518, 1375, 1005) showed a tendency to that decline in 2 times, which according to Jørgensen is characteristic for diabetes. After the first bold decline the sugar curve becomes flatter, the fasting values being reached somewhat later. Besides one patient with essential hypertension there are two with hypertension + metabolic disturbance, and two patients with hypertension + arteriosclerosis. Besides endocrine disturbances, the magnitude of the blood volume, the degree of repletion of the carbohydrate depots etc. certainly assert themselves here, too, whence the shape



of the curve scarcely can be put into primary relation with the hypertonic condition.

Previous investigations in the carbohydrate metabolism in hypertonics have disclosed somewhat different conditions. Thus Brems after peroral administration of glucose to patients suffering from hypertension without kidney disease found a normal blood sugar curve, whereas the alimentary blood sugar curve of patients with hypertension + kidney disease revealed a tendency to protracted hyperglycemia. In contradistinction to this Schweers in patients with essential hypertonia found diabetic curves after peroral administration of glucose, and Jansen likewise reports having observed a diabetic course of curve in case of nephrosclerosis and vascular hypertonia, but normal conditions in case of chronic nephritis. It may further be mentioned that glycosuria according to Kylin's investigations occurs in 20 per cent of hypertonics, as an expression of a disturbance of the carbohydrate metabolism.

With regard to the difference between capillary and venous blood the conditions were found to correspond to those in the normal, i. e. a great difference in the high values. In those cases where the decline of the curve is protracted, it may be concluded that the sugar compensation must take place more slowly, the mean error, however, is so great that the proportion does not manifest itself by the blood sugar determination. In these cases no hypoglycemic after-fluctuation was obtained within the experimental time.

As to the urine, glycosuria subsequent to the injection was detected in all these patients just as in the normal, and contrary to Polack and Harpoth's findings, these authors reporting that they did not find glycosuria in any one of the hypertonics who were treated with glucose in similar doses. The sugar content of the urine discharged immediately after the experiment amounted to from 1.6 to 9.3 g. i. e. from 3.2 to 19 per cent of the injected quantity. In 1 case (No. 1375), moreover, the sugar content of the urine discharged during the subsequent 20 hours amounted to 1 g.

The water content of the blood despite the different pathogenesis of the hypertension was found to be fairly the same in all these patients. Just as in the normal, a temporary increase of 2 per cent of the water content of total blood was found immediately after the injection, the water percentage subsequently returning

rapidly to the initial values, eventually to a little lower values. The water content of the plasma presented corresponding fluctuations. Concerning the fluctuations in the percentage of cell volume and hemoglobin the author refers to the preceding account.

The uniform reaction of the different forms of hypertonia to injections of large doses of glucose manifests itself also by the conditions of the blood pressure, a decrease of the systolic blood pressure being found, which averagely was much more pronounced than in the normal. In 2 cases a temporary minor increase (up to 10 mm.) was found immediately after the injection, and such an increase was also observed by Martinetti after similar dosage and time of injection, and by Hess, Bürger and Hagemann after minor doses.

In 4 of the patients the decrease commenced in the course of a few minutes after the injection, whereas, in 3 cases, it did not commence before 10—15 minutes had elapsed. In 5 of the patients the decrease of the blood pressure was fairly pronounced (25—35 mm.), whereas, in 2 cases, it was slight (5—10 mm.) and, in 1 case (hypertension + arteriosclerosis), no decrease of the blood pressure was found. The fluctuations of the diastolic pressure were but slight (5—10 mm.). By continual measurings it was detected that the return of the blood pressure to the initial values, in most cases was accomplished within the 3 experimental hours, and in the few cases where this did not happen, the initial values were reached almost always 3 hours after the termination of the experiment. An ulterior effect of the glucose was not detected, the blood pressure thus always being unchanged 24 hours later.

For the sake of comparison with these findings I shall briefly record the result of Polack and Harpoth's work. These authors likewise found a decrease in the systolic blood pressure after injection of 100 cm<sup>3</sup> of a 50 % glucose solution in the course of 1—2 minutes. In 15 of the 20 patients examined it occurred rapidly, whereas, in the remaining 5, it did not occur till 10—20 minutes had elapsed. In 17 of the patients the decrease of the blood pressure was fairly pronounced (about 30—40 mm.), in 3 cases, however, being but slight (5—10 mm.). Here, too, the action on the blood pressure seemed to be fairly independent of the hypertension being essential or secondary, and it generally persisted throughout the entire observation time (up to 100 minutes). A distinct relation between

the obtained decrease of blood pressure and the initial values was not detected, even though a tendency towards a more pronounced decrease might be perceptible in cases with higher initial values.

The reaction to intravenous glucose injection apparently being fairly uniform in normal and hypertonic individuals, it may be assumed that the cause of the decrease of blood pressure is the same, too, but that the decrease merely is greatest in individuals presenting higher initial values.

An explanation of the increase of the blood pressure immediately after the injection is not known but, possibly, it is of psychic, i. e. nervous, origin. On the other hand, many theories have been set forth with regard to the origin of the decrease of the blood pressure, the conditions are not quite cleared up, however. Harris and Mc Loughlin in hypertension of different genesis found an increase of the viscosity, and some authors declare that the decrease of blood pressure must be ascribed to a decrease of this viscosity, whereas others opine that it is due to changes in the secretion of cerebrospinal fluid.

The present work has shown, however, that changes in the water content of the blood and, hence, in the viscosity of the blood cannot be of any importance for the decrease of the blood pressure. Nor was that to be anticipated, since the viscosity of the blood according to recent investigations scarcely has much importance for the blood pressure; thus Ask-Upmark has pointed out that hypertension fails to appear in case of phosgene poisoning which is attended by a pronounced increase of viscosity.

Among the works treating of this decrease of the blood pressure may be mentioned investigations by Wollheim and Brandt who, after intravenous injection of 10 cm<sup>3</sup> of distilled water, demonstrated a decrease of the quantity of circulating blood and, by counting the erythrocytes and determining the hemoglobin percentage, found hydremia persisting for from 1 to 2 hours. The normal blood pressure was found to be unchanged, whereas the hypertension decreased, and from these findings they infer that the decrease of the blood pressure after intravenous injection of glucose is due to the injected water, and not to the sugar which is said to have no osmotic effect.

Several other investigations indicate, however, that the presence of glucose is of no little importance for the fluctuations of the

blood pressure, since the glucose exerts a dilating action on the vessels. Thus Handovsky and Meyer under the action of glucose found dilatation of isolated vessels, while Meyer and Weil have seen a salutary effect of glucose injection in intermittent claudication and other angiospastic conditions, which according to Weil and Mészáros are attended by dilatation of the capillaries. A reduction of the minute volume of the heart might be thought to bring about a temporary decrease of the blood pressure, but such a reduction scarcely does happen. On the contrary, Hildebrandt and Kisch have experimentally demonstrated a pronounced increase of the minute volume, which is explained by an increase of the quantity of blood as well as by a stimulation of the heart function corresponding to the coronary perfusion greatly increased after *intravenous injection of glucose*, which was demonstrated experimentally also by Stoland and Ginsberg. As a consequence of the effect of the glucose on the minute volume and vessels experiments have likewise disclosed an increase in the perfusion of the kidneys which, as was mentioned, may possibly be of importance for the diuretic effect.

That the decrease of the blood pressure must be assumed to be essentially due to vascular dilatation, is supported by the fact demonstrated by Weil, Meyer, Opitz, and Raegner that, in hypertension attended by arteriosclerosis, it is very slight and eventually fails to occur. This was also observed in the present work.

Besides the glucose directly giving rise to vascular dilatation, other factors certainly must also play a part. Thus it may be mentioned that Meyer and Handovsky found changes of the plasma colloids and particularly of the structure of the cholesterin, which is presumed to cause a change of tonus of the vessels, eventually via the sympathetic nervous system. Moreover, the fluctuations of the blood sugar probably are of importance for the decrease of the blood pressure. Thus Brems and Holten in normal and diabetic individuals, who had received insulin, found an increase of the systolic blood pressure (20—30 mm.), if there appeared hypoglycemic symptoms, but not when such symptoms failed to appear. This increase of blood pressure disappeared after injection of glucose. It is assumed that the increase of the blood pressure is due to increased adrenalin excretion from the adrenals on account of the insulin giving rise to central irritation. This irritation probably,

or at any rate partially, is due to the blood sugar. Of importance for the blood sugar regulation partially is the internal secretion of the pancreas, the influence of other endocrine organs, particularly the thyroid gland and the chromaffin system, the action of both these being opposed to that of the pancreas, partially the nervous system, and here particularly the sympathetic nervous system. The normal blood sugar regulation seems to be due to changes in the blood sugar concentration affecting one or several of these factors. Possibly the observed decrease of blood pressure is in part due to the injected glucose affecting the balance between the antagonistic hormones adrenalin and insulin so that the increase of insulin excretion from the pancreas coincides with an inhibition of the adrenalin excretion from the adrenals. That the induced decrease of blood pressure at any rate in part must be attributed to the hormones is also supported by the fact that the fluctuations of blood pressure do not coincide with the fluctuations of blood sugar but lag somewhat after these, corresponding to a change in the hormone balance of the blood which regulates itself only after a certain lapse of time.

According to recent hypertension theories, however, the adrenalin does not play so important a part for the maintenance of the blood pressure as was hitherto assumed. Therefore it is tempting to parallel the decrease of blood pressure with these theories. When renin forms in the ischemic kidneys, it might be thought that, inversely, the induced strong blood perfusion of the kidneys entails a temporary decrease of the formation of renin.

Whereas it is probable that the slight decrease of blood pressure in the normal predominantly is due to a direct action of the glucose on the vessels, eventually concurring with a temporarily decreased adrenalin balance in the blood, it is possible that other causes also are of importance for the decrease of blood pressure in hypertonics.

### Conclusion.

The result of these experiments with intravenous injections of 100 cm<sup>3</sup> of a 50 % glucose solution applied to hypertonics thus is that the fluctuations in the sugar and water content of the blood — regardless of the kind of hypertension — does not differ essenti-

ally from those observed in the normal, and that the decrease of the blood pressure cannot be assumed to be due to an osmotic action.

### Summary.

Previous examinations of animals as well as of human beings who had received intravenous injections of hypertonic glucose solutions generally disclosed more or less pronounced transitory hydremia. However, this increase of the aqueous content of the blood is always determined indirectly and, frequently, on a material of patients in whom a spontaneous dilution of the blood is not quite excluded. The hypertonic glucose solution is frequently employed in the so-called osmotic therapy the theoretical base of which is the hygroscopic action of the hypertonic solution and the hydremia produced thereby.

The scope of the present work particularly was to find out, by direct determination of the aqueous content of the blood, in how high a degree absorption of fluid in the vascular system takes place in the normal after intravenous injection of hypertonic glucose solution, and a corresponding examination of the conditions of hypertension, one of the pathological conditions on which the osmotic therapy is reported to be of salutary effect. Further, both the proportions of blood sugar and blood pressure were examined after such an injection.

In all the cases was used injection of 100 cm<sup>3</sup> of sol. glukosi Leo 50 % in the course of 2—3 minutes. In none of the cases did any complications occur in sequel to the injections. The blood sugar fluctuations were determined at the same time both in capillary and venous blood with Hagedorn and Norman Jensen's method. The examinations of the aqueous content of the blood were performed a. m. Schwensen the principle of which is weighing of the blood prior and subsequent to drying in a vacuum exsiccator. Moreover, the cell volume percentage of the blood was determined with van Allen's hematocrit, and the blood pressure was measured with a mercury manometer and the English-American standard technic. The discharge of sugar in the urine was examined with Almén's solution and Lohnstein's saccharometer. All the determinations were duplicate determinations, and the mean error was calculated.

The examinations were carried out on fasting test persons both before and immediately after the glucose injections, and then 10, 25, 40, 60, 90, 120, 150, and 180 minutes later. The blood pressure was moreover controlled 3 and 24 hours after the termination of the experiment. The diuresis during the following 20 hours was measured, and the discharge of sugar was determined. In isolated cases the hemoglobin per cent was likewise determined in capillary blood (Zeiss hemometer) during the first hour after the injection.

The material of normal persons consisted of 8 apprentice hospital nurses aged 23—31 years. The blood sugar showed an initial increase up to 400—500 mg. % and a subsequent decrease to the fasting values in the course of 90 minutes. The glucose level was found to be higher in capillary than in venous blood, being most pronounced in the high blood sugar concentration, where the difference amounted to up to 49 mg. %, as an expression of considerable and rapid purification of the blood from sugar in the tissues. In all the cases glucosuria was observed immediately after the experiments, and the discharge of sugar amounted to from 4.2 to 10.8 g. In isolated cases there was an additional discharge of very little sugar (1—1.5 g.) during the next 20 hours. In several cases increased diuresis was observed.

The aqueous content of both total blood and plasma was found to have increased by about 2 per cent, and this slight hydremia disappeared in the course of about 60 minutes. The reason why no dilution of the blood is observed besides that which can be explained by the injected quantity of water probably is the very rapid sugar compensation between blood and tissues in connection partly with the rapid excretion of the water through the kidneys and partly by its retention in the tissues during the deposition of the glucose. The percentage of the cell volume of the blood accordingly fluctuated by about 3 vol. %. The blood pressure presented but slight fluctuations, i. e. in the majority of cases a minor transitory decrease of the systolic pressure (5—10 mm.), eventually preceded by a slight increase immediately after the injection. 3 and 24 hours later the blood pressure was always found to be normal.

The hemoglobin percentage whose determination is encumbered with fairly great errors, decreased by up to 19 per cent immediately after the injection, subsequently rising again. What is responsible

for this fluctuation is not known, possibly, however, there is a question of a change in the distribution of the blood.

The hypertension material comprises 8 patients with essential or secondary hypertension. The proportions of blood sugar were found to be averagely the same as in the normal, though, in 5 cases, there was a tendency to diabetiform course of the curve. The discharge of sugar immediately after the experiments amounted to from 1.6 to 9.3 g., and in 1 case, 1 g. during the subsequent 20 hours. Nor was there in this series of experiments detected any osmotic effect of the glucose, the fluctuations in the aqueous content of the blood — regardless of the nature of the hypertension — not deviating from the normal, and the same holds for the cell volume and hemoglobin percentages. In several of the 7 patients the systolic blood pressure presented a fairly pronounced decrease, eventually preceded by a minor increase immediately after the injection. In one case of hypertension + arteriosclerosis no decrease was observed. The initial values were in most cases reached 3 hours after the termination of the experiments, and were always found after 24 hours.

The pathogenesis of these fluctuations in the blood pressure are discussed. The initial increase probably is of nervous origin. The slight decrease of the blood pressure in the normal probably is chiefly due to a direct action of the glucose on the vessels, eventually in connection with a temporarily decreased adrenalin level in the blood, whereas it is possible that other factors such as changes in the formation and discharge of renin moreover are of importance for the decrease of blood pressure in hypertonics.

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## Thrombosis of the Internal Carotid Artery.

A Clinical Study of Nine Cases diagnosed by Arteriography.

By

PER OTTO ANDRELL.

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Although thrombosis of the internal carotid artery does not seem to be uncommon, this condition is rarely diagnosed during life. The reason responsible for this fact is the difficulty to demonstrate the lesions which is done by means of arteriography, a method as yet not very widely used.

The cases diagnosed arteriographically are specially interesting, because they may be studied more deliberately and in greater detail than the cases diagnosed at autopsy in which death had occurred frequently a short time (at the end of a few days, sometimes even at the end of a couple of hours) after the onset of the catastrophes.

The author's study of the literature revealed that there are all in all 23 cases of thrombosis of the internal carotid artery published which had been recognized by arteriographic examination. The cases in which the lesions were due to extraarterial insults such as traumas, tumours, surgical intervention *a. s. o.* were not taken into consideration.

In 1936 Egas Moniz in collaboration with Lima and Lacerda described four cases of thrombosis of the internal carotid artery of which one case had been observed as early as 1931. Löhr published the description of three cases. Schimidzu in 1937 reported one case.

In 1938 Chao in collaboration with Kwan, Lyman and Loucks published two cases, Riechert three cases and Siegert two cases of this type. Sörgo described eight cases.

The material which will be reported in the following covers six cases which the author studied closely at the Neurological Clinic, and three cases which were treated at the Neurosurgical Clinic of the Serafimer Hospital in Stockholm. Grateful appreciation is hereby expressed to Professor Herbert Olivecrona for the clinical data on the three last mentioned cases.

Diagnosis was established in all cases by means of arteriography. The respective roentgenological examinations were performed by Docent Erik Lysholm and his collaborators at the roentgenological services of the Serafimer Hospital, Stockholm.

**Case 1.** — George L., born in 1893, street-car conductor, was treated at the Neurological Clinic (Record 311/1938) and at the Neurosurgical Clinic (Record 410/1938). The patient had been in good health until the beginning of the year 1937 when attacks of headache set on which were of short duration and localised in the left portion of the crown of the head. The attacks occurred in intervals of about one month. In April 1938 the headaches became more intensive and constant. There was acute onset of aphasic troubles. He was admitted to the Neurological Clinic and at a later period referred to the Neurosurgical Clinic. His consciousness was clear, but he appeared depressed. He exhibited symptoms of aphasia. He understood most of what was said to him, but not everything. He obeyed fairly well simple commands, but could not obey commands of a more involved nature. He had difficulty in word-finding and at times used wrong words without noticing it. His attention was good. He exhibited easily fatigue. Apart from a slight blurring of the borders of the disks and from a weakness of the right lower facial branch, the neurological examination did not reveal anything unusual.

The roentgenograms of the skull and the encephalogram did not reveal any evidence of pathology.

On exposing the left common and internal carotid arteries for the purpose of arteriographic examination it was found that the internal carotid artery was pulseless at a point about 3 cm above the bifurcation and that it was narrower than normal. The findings at the arteriographic examination were the following: the needle lay in the internal carotid artery. The contrast medium entered the artery as far as 1 cm and from that point on, and within the adjacent area of about 2 cm in length the column formed by the contrast medium showed an irregular narrowing. From that point on the contrast medium did not fill the artery any further, but flowed back into the external carotid artery the branches of which did not exhibit any alterations. Arteriographic examination evidenced the presence of a

narrowing and of an obliteration of the internal carotid artery immediately above the point where it branches off from the carotid artery.

A segment of the artery was excised and found to be thrombotic. The pathological-anatomical examination was carried out by Prof. Hilding Bergstrand who reported the following: »Cross section of the artery showed the formation of a thrombus in the lumen which, however, did not completely block it. The thrombus exhibited organization and recanalisation and therefore must have been of old standing. The intima was grossly thickened. In the adventitia and in the periarterial tissue there was presence of considerable inflammatory cell infiltration, especially of round cells, but quite a lot of leucocytes were also detected. In spite of this inflammatory alteration the picture is not similar to that of periarteritis nodosa.»

Apart from a mas'ic curve of 11221100 the spinal fluid did not reveal anything unusual. The Wasserman test was negative both for the spinal fluid and for the blood.

The blood-pressure was 180 systolic, 125 diastolic. The heart showed inconsiderable enlargement, but was otherwise of normal appearance. The condition of the patient improved gradually. At the end of about a year he was able to take up work again and got a job in a bus-garage.

*Summary:* Report of the history of a street-car conductor born in 1893. Since the beginning of the year 1937 he complained of headaches on the left side which occurred in attacks. In April 1938 there was acute onset of aphasia and evidence of weakness of the right lower facial branch. Arteriographic examination revealed thrombosis of the left internal carotid artery. On pathological-anatomical examination the presence of an organized thrombosis, of a thickening of the intima, and of inflammatory alterations of the media and adventitia was demonstrated. The patient regained his working power at the end of one year.

**Case 2.** — Erik J., born in 1906, workman in a paper-mill, was treated at the Neurological Clinic (Record 544/1938). The patient does not know of any hereditary nervous or mental diseases existing in the family. His health had previously been good. In 1920 when leaning over the railing of the shaft of a lift his chest was squeezed in by a lift going downwards. He fell head foremost about three meters deep and contracted a trauma of the skull. He was unconscious for some time. At the end of a month he was able to take up work again and felt completely restored.

In the beginning of the year 1930, he was subject to attacks similar to hemicrania. Headaches occurred which lasted from 20 to 30 minutes and which were followed by visual disturbances which he called »glistenings» and by sensations of discomfort. In the spring of the year 1934 these troubles occurred more frequently. One morning, about midsummer of the same year, he woke up at 5 o'clock with a severe headache, fell asleep

again, and woke up once more at 8 o'clock. The left side of his body was completely paralysed, his face was distorted; he had a headache which was most pronounced on the right side. There was absence of visual or other disturbances.

At the examination at the Serafimer Hospital, Stockholm, six weeks after the onset of this attack, the patient exhibited on the left side a very pronounced spastic hemiparesis with some motility of the lower extremity maintained. The muscular reflexes in the arms were equally strong on both sides. On the left side, there was presence of symptoms suggestive of foot clonus and of exaggerated patellar reflex. The Babinski test was negative on this side. There was further paresis of the facial and hypoglossal nerves on the left side and evidence of a left-sided hemianesthesia. The abdominal reflexes were absent on the left side and the cremasteric reflexes were weak on this side. The visual acuity and fields, the pupillary reflexes as well as the eyegrounds showed nothing unusual.

No evidence of pathology was to be seen in the roentgenogram. The encephalogram revealed a slight lateral displacement of the lateral ventricles and the septum pellucidum, a few millimeters to the right of the medium line. The position of the third ventricle was slightly oblique. Corresponding to the cella media the right lateral ventricle was larger than the left.

Examination of the cerebrospinal fluid showed nothing unusual. The Wasserman test of the blood and of the cerebrospinal fluid was negative. The sedimentation rate was 25 mm after 1 hour. The urine was normal. The blood-pressure was 105 systolic and 70 diastolic.

The patient's condition improved subsequently and at the end of four months he was able to walk. He was, however, not able to take up his work and lived on a sick-pension.

In the summer of the year 1933 he began manifesting epileptic seizures. On one occasion he felt a twitch in the left side of his face. He also felt «rather queer». At that time he had no spells of unconsciousness and was able to answer when spoken to. Sometime later he was subject to acute attacks of unconsciousness associated with tonic spasms and tongue-biting. These attacks which were not preceded by aura were accompanied by a complete amnesia and occurred about once a month.

In the autumn of the year 1938 he came to the Neurological Department for examination.

On admission he manifested a moderate spastic hemiparesis of the left side. The muscle power of the left arm was considerably reduced, of the left leg moderately and was weakest in the left foot. He was able to walk with support of a stick. He walked with outstretched left leg moving it by circumduction and with the left foot twisted into talipes equinus position. While he was walking the leg was subject to spasms. The patient moved along holding his left arm across his chest and flexing his fingers towards the palm of his hand; his thumb was turned inwards.

On the paretic side there was presence of exaggerated muscular reflexes

and of spinal automatism as well as of positive Babinski, Rossolimo and Trömmner signs. On the left side «décomposition des mouvements» was observed. The Romberg test was negative. Superficial sensation as well as deep sensation was grossly reduced on the left half side of the body and there was absence of abdominal and cremasteric reflexes on this side. On the left side there was manifestation of signs suggestive of facial paresis of the central type and evidence of paresis of the hypoglossal nerve.

The visual acuity of the left eye was normal, of the right eye it measured 9/10. The visual fields and the eyegrounds were normal.

The encephalogram revealed displacement of the septum pellucidum and of the third ventricle about  $\frac{1}{2}$  cm to the right of the median line, dilatation of the right lateral ventricle which was drawn upwards in a lateral direction. The left temporal horn was in its normal position. The shrinking on the right side had considerably increased since the last examination.

On arteriographic examination in the course of which thorotrast was injected into the common carotid artery, the contrast medium filled only the branches of the external carotid artery. On palpation the internal carotid artery was found to be firm, narrower than under normal conditions and pulseless.

Examination of the cerebrospinal fluid revealed nothing unusual. The Wasserman test was negative for both blood and cerebrospinal fluid.

In the right temple area there was presence of a pigment naevus of the size of a ginger-head nut resembling a chloasma and of pigmentation of the same type of the size of a man's hand below the left shoulder area and on the right instep. There was also evidence of Dupuytren's contraction.

The clinical examination of the heart revealed a systolic murmur above the pulmonary artery, and the roentgenological examination a general enlargement. Electrocardiographic examination showed right ventricular preponderance as well as intraventricular conduction block. The blood-pressure was 120 systolic and 85 diastolic. Somatic examination showed otherwise normal conditions.

Apart from a certain fussiness and from an inclination to dwell tediously on the same subject coexisting with irritability, his mental functions were normal.

Concluding it should be stated that he was right-handed and that there was absence of aphasic symptoms.

*Summary:* Report of the history of a workman employed in a paper-mill who was born in 1906 and who had been subject to a severe trauma of the skull in 1920. Somewhere about 1930 there was onset of attacks similar to hemicrania. In 1934 while the patient was asleep hemiparalysis of the left side occurred. He came to the neurological services of the hospital and his examination revealed the following: on the left side presence of positive Babinski

was evidence of transient attacks of paresis of the right arm and visual disturbances. In February 1939 he exhibited aphasia. He was admitted to the hospital in March. At that time there was presence of flaccid paresis of the right arm and of both legs. In these extremities there was absence of muscular reflexes. The Babinski sign was negative on both sides. The skin was dry and showed pigmentation, in both feet and in the right hand there was evidence of edema. Arteriographic examination revealed occlusion of the left internal carotid artery. Exitus a few weeks later. The post-mortem examination showed the presence of thrombo-angiitis obliterans in the arteries of the brain, chiefly in the right middle artery.

**Case 4.** — Maria N., born in 1902, married, came for treatment to the Neurological Clinic (Record 595/1940). She had previously enjoyed good health. On September 2 she was found lying prostrate on the floor in her flat. Her right side was paralysed and she was aphasic. She vomited several times. She was brought to Sabbatsberg Hospital. On admission she had slight cramps in the left arm and in the left leg. The right side was paralytic. The Babinski sign was positive on that side and there was presence of patellar clonus. The facial and pharyngeal musculature of the right side was paralysed. The tongue deviated towards the right. On the right side of the body there was absence of superficial as well as of deep sensation. Towards the end of the month the patient gradually regained motility of her right leg. The arm was paralytic. She was still aphasic.

On October 17 she was admitted to the neurological services of the Serafimer Hospital.

Motility of the paretic side of the body was unchanged. Owing to the presence of a very pronounced spasticity, all passive movements of the right arm or leg were at that time impossible. Foot clonus as well as patellar clonus and positive Babinski and Rossolimo signs were present on the right side. There was also evidence of right-sided facial paresis. The patient was unable to lift her right shoulder. The tongue deviated to the right. Appreciation to pin pricks was weaker on the right side than on the left with exception of the skin of the face where conditions were reverse. Coordination was normal on the left side, on the right side it could not be tested. The patient exhibited aphasia associated with alexia and agraphia. Roentgenographic examination of the skull revealed nothing unusual. On encephalographic examination the following was found: no dislocation of the ventricular system. The volume of the left lateral ventricle was as a whole somewhat larger than that of the right. Otherwise there were no alterations of the lateral ventricles. Frontally, on the right side, several sulci were detected, which were wider than normal.

Arteriographic examination revealed a constriction of the left internal carotid artery to the shape of a cornet immediately above the

point where it branches off the common carotid artery. In this area the contrast medium indicated small irregularities. The contrast medium filled the internal carotid artery within an area of about only 2 cm in length; at this point there was complete obliteration and the contrast medium flowed back and entered the external carotid artery and its branches. Obliteration of the left internal carotid artery immediately above the point where it branches off the common carotid artery was recognized.

The cerebrospinal fluid was normal.

The patient's physique was normal. There was no evidence of alterations of the skin.

Physical and electrocardiographic examination of the heart revealed nothing unusual. The blood-pressure was 120 systolic and 80 diastolic. Roentgenographic examination of the heart and the aorta showed normal conditions. The presence of sclerotic alterations of the blood vessels on the left forearm and lower part of the left leg could not be proved roentgenologically.

Oscillometric examination of the calves and the upper arms which was made by Dr. Ragnar Bringel showed the following; »The maximal amplitude was considerably reduced with no difference on the two sides. Although there was no obvious sign of cardiac deficiency, the curve suggested anatomical alterations of the arterial walls of the (symmetrical) type such as the undersigned had only seen in five cases of pseudoxanthoma elasticum. (In endarteritis obliterans, juvenile arteriosclerosis and morbus Buerger there is always a difference of amplitude between the respective extremities.)»

The Wasserman reaction was negative for both blood and cerebrospinal fluid. The sedimentation rate measured 8 mm after 1 hour.

Once, during her hospitalization, the patient complained of pains over the precordium which set on in attacks and which were of the anginal type. These symptoms were accompanied by severe pains in the right leg which appeared somewhat anemic. The blood-pressure was then 150 systolic and 100 diastolic. The pulse was normal. The routine clinical examination of the heart did not reveal anything unusual...

The patient left the hospital in the middle of December. At that time she was able to walk with support. The paresis of the right arm had but inconsiderably improved. The aphasia was unchanged.

*Summary.* Report of the history of a married female born in 1902. In September 1940, the patient manifested acute onset of hemiparalysis of the right side and of aphasia. She came to the hospital for treatment. The Babinski sign was positive on the right side. There was presence of paralysis of the facial and pharyngeal musculature and of the accessory nerve on the right side. Hemianesthesia was present on the right side in the trunk and on the left side in the face. The patient exhibited aphasia accompanied by



On October 31, arteriography of the internal carotid artery was performed which revealed the following: the contrast medium entered the carotid artery as far as the siphone, but not further. Part of the contrast medium flowed back into the common carotid artery. Arteriographic examination proved that the right internal carotid artery was obstructed in the area of the siphone.

On November 4, signs suggestive of a left-sided hemianopsia were observed which, however, could not be verified a few days later.

Towards the end of the month embolism or thrombosis of the right central artery was diagnosed.

His condition improved gradually. The aphasia was recognized to be of the Broca type accompanied by literal paraphasia and his speech was brief and limited to a vocabulary as is used for the wording of cables. He was able to read and write fairly well. The aphasia improved to such a degree that he was able to talk tolerably well at the end of three months. He was right-handed. At that time he was able to walk without support and held the left leg straight moving it by circumduction. There was still presence of a pronounced paresis of the arm and a paralysis of the hand. The facial paresis was unchanged. The muscular reflexes in the left arm and in the left leg were increased. On the left side there were positive Babinski and Rossolimo signs. The patient's physique was normal. On his left hand he exhibited a pigment naevus of double the size of a 5 öre (halfpenny) coin.

The heart showed normal conditions. Roentgenological examination of the heart and the aorta did not reveal anything unusual. The electrocardiogram was normal. The blood-pressure was immediately after onset of the disease 145 systolic and 95 diastolic (pulse rate 62), fell subsequently to 120 systolic and 70 diastolic, and rose at the end of three months to 160 systolic and 105 diastolic (pulse rate 100).

The cerebrospinal fluid showed 16 monocytes/3.2 cm. Otherwise nothing unusual was observed. The Wasserman reaction was negative both for the blood and the cerebrospinal fluid. The cholesterin determination of the blood yielded a value of 217 mg %. The sedimentation rate was 7 mm after 1 hour.

*Summary:* Report of the history of an engineer, born in 1908. Since September 1940 the patient exhibited neurasthenic symptoms. Towards the end of October there were periodic attacks of aphasia of short duration. On October 30, he manifested suddenly hemiparesis of the left side. He was admitted to the hospital. The Babinski sign was positive on the left side, possibly also on the right side. The muscular reflexes in the extremities were symmetrical. There was evidence of left-sided central facial paresis. Paralysis of vertical ocular movements was suspected. The patient showed signs of

aphasia of the Broca type. On November 4, hemianopsia occurred on the left side. Towards the end of November, embolism or thrombosis of the central retinal artery was recognized. Two months later there was amelioration of the hemiparesis as well as a slight improvement of the aphasia. The arteriographic examination revealed occlusion of the right internal carotid artery.

**Case 6.** — Emma O., born in 1892, married, was admitted to the Neurological Clinic (Record 76/1941). The patient denies nervous diseases in the family. Her mother and one brother died of an organic disease of the heart. In the year 1917 she had scarlet fever accompanied by otitis on the right side. In the year 1937 a slight hypertonia was recognized. In the course of that year she complained of heart troubles which manifested themselves in difficulty in breathing, heart throbbing and sensations of fatigue. Towards the end of July 1940 she suddenly fell prostrate to the ground. Most likely she was unconscious for some time, but when she recovered she was able to walk home alone, which took her about 20 minutes. After having come home she complained of fatigue and pains in her arm. These troubles disappeared after 24 hours. From that time on she was completely free from complaints until the month of October of the same year when she manifested increasing weakness of the right arm accompanied by a sensation of awkwardness. She had great difficulty in eating with her right hand and was unable to work. During the following period of time her condition improved at times considerably and she was able to eat without having to be helped and could also do the house-hold work alone. Since the middle of December, however, she had no strength in her right arm. Since October 10, she had five attacks of loss of speech power. She understood everything that was said to her, but was unable to speak for some minutes. At times she could not complete a sentence which she had begun. During such spells her memory was most likely impaired. Her consciousness, however, was apparently not disturbed. Since October her vision impaired so grossly that she was unable to read in November. Since the beginning of November she had the sensation of a roaring noise in her head resembling the roar of an engine. In the middle of December there were sudden exacerbations with headaches localized in the area above the left eye and further impairment of vision. The weakness of her right arm increased and the right leg began to feel awkward. She complained of attacks of vertigo. At one occasion the attack was so severe that she fell down.

After having been treated at a hospital in her native town, she was submitted to the Neurological Clinic on January 21. On admission she felt tired and drowsy. Her concentration power was impaired, the reaction time was prolonged and her memory was poor. She showed cortical aphasia of the Broca type associated with agraphia, alexia and acalculia. She exhibited on the right side a slight hemiparesis which was more pronounced

in the arm than in the leg, the muscular reflexes on the right side were more pronounced than on the left side. Grasset's and Souques' phenomena were positive on the right side. Trömner, Babinski and Rossolimo signs were negative on both sides. There was absence of abdominal reflexes. The lower part of the facial area on the right side was slightly paretic. Further, a slight deviation of the tongue to the right was observed. Apparently, there were no disturbances of sensation. There was manifestation of Romberg's sign with tendency to fall backward — to the right. Adiadokokinesis was present on the right side as well as a right-sided homonymous hemianopsia. Since her childhood she had been manifesting a slight strabismus with gross impairment of vision on the right side. Examination of vision showed: in January, left: 2/10, a month later 9/10. The eyegrounds did not show anything unusual and the pupils reacted normally.

Roentgen examination revealed apart from a relatively short and high skullcap nothing unusual.

The findings at the arteriographic examination of the left carotid artery were the following: the point of the needle penetrated 1 cm deep into the internal carotid artery. On injecting the contrast medium, the medium filled only the distal area of the internal carotid artery within an area of about  $\frac{1}{2}$  cm in length above the point of the needle. The extreme end of the contrast medium column showed irregularities and was frayed. There was back-flow of the contrast medium into the common carotid artery. The roentgen examination showed obstruction of the inferior portion of the internal carotid artery.

The cerebrospinal fluid was normal.

The blood-pressure was 195 systolic and 125 diastolic. The electrocardiogram did not show anything unusual. The roentgenogram of the heart and the aorta was normal.

At the roentgen examination sclerotic alterations of the walls of the arteries of the lower leg — especially on the right side — were recognized.

The Wasserman reaction was negative both for the blood and for the cerebrospinal fluid. The sedimentation rate was 65 mm after 1 hour. The determination of the cholesterin percentage of the blood yielded 182.5 mg %, 221 mg\*%.

The patient was right-handed.

*Summary:* Report of the history of a female, born in 1892. In 1937 hypertonia was recognized. In July 1940, she suddenly lost consciousness and subsequently complained of weakness and pains in the right arm lasting for a day. In October recurrence of weakness of the right arm. Since the middle of October onset of seizures of aphasia and impairment of vision of the left eye. In the middle of December, renewed gross impairment of vision and complaints of headaches above the right eye. A right-sided hemiparesis

developed. She was admitted to the hospital. The Babinski sign was negative. There was presence of facial paresis on the right side. Paresis of the hypoglossal nerve was recognized. Homonymous hemianopsia was present on the right side. The arteriogram revealed occlusion of the left internal carotid artery. Sclerotic alterations of the arteries of the lower leg were visualized in the roentgenogram.

**Case 7.** — Gustav J., born in 1904, joiner, was treated at the Neurosurgical Clinic (Report 1/1958). Concerning family diseases, nothing of interest is to be reported. He had enjoyed good health. He may have been left-handed. He threw stones and drove in nails with his left hand, but he wrote with his right hand. In the middle of June 1937, he suddenly experienced difficulty in writing. He skipped over syllables and also made other mistakes. One morning, in the end of June, he woke up and was unable to speak. He could only say «yes». His right arm and leg felt clumsy. This feeling was strongest in the arm. He did not limp and was able to eat with his right hand, although with difficulty. At the end of a few days, there was gradual amelioration of his power of speech. The feeling of clumsiness in his right leg regressed and disappeared completely in the middle of July; the clumsy feeling in his right arm subsided more slowly. In the beginning of October, renewed loss of power of speech accompanied by clumsiness of his right arm. These symptoms subsided gradually, but did not disappear completely. During the first weeks in July the patient complained of severe headaches on the left side, localized in the temple area and in the nape. The pains set on in attacks several times during the course of a week and the attacks were from three to four hours duration. In the middle of August, he complained of a sudden seizure of blindness of the left eye. He was on the verge of fainting and saw everything blurred for a few minutes, but subsequently he was able to see clearly again. These symptoms manifested themselves periodically, at times twice a day, but, as a rule, not more frequently than all in all four times a month.

On January 1, he was submitted to the Neurosurgical Clinic. On admission the patient showed a slight reduction of strength in the right arm and leg, but no definite evidence of paresis could be demonstrated. The muscular reflexes in the right leg were somewhat increased. Mendel-Bechterew and Gordon signs were positive on the right side. The Babinski sign was negative on both sides. The abdominal reflexes were weaker on the right side. There may also have been presence of a slight central facial paresis of the right side. The patient could not lift his right shoulder with normal strength. The pupils as well as the eyegrounds did not show anything unusual. His mental functions were normal. His arithmetical powers were poor. He exhibited a slight agraphia.

Roentgen examination of the skull showed a sclerotic corpus pineale 2 mm to the left of the median line.

On encephalographic examination the left lateral ventricle was found to be enlarged.

The left internal carotid artery was exposed for the purpose of arteriographic examination and the following conditions were found: the artery superior to the carotid sinus was changed to a fibrous string about the breadth of a goose-quill. No blood could be withdrawn. On an attempt to perform arteriography of the common carotid artery, the whole amount of the injected contrast medium flowed into the external carotid artery. Arteriography of the right side showed that the contrast medium filled the anterior and medial cerebral arteries of both sides. (see Figs. 3—4). The blood vessels were normally situated and did not show any dislocation. Three days later a segment of the obliterated artery of about 1 cm in length was excised.

The pathological-anatomical examination was carried out by Professor Hilding Bergstrand who reported the following: "The adventitia of the blood vessel showed a thickening and an increase of the collagenic substance which presented coarse hyalinised fibrils. The adventitia showed more abundant vascularization than under normal conditions. Numerous leucocytes were seen in the minute vessels and some of these cells infiltrated even the connective tissue of the adventitia. When staining the elastin the media showed fleckiness; this instance may be accounted for by a difference in the quantity of elastic substance which was present in the different areas, in some areas there was more quantity present whereas in others less. The media showed further a slight infiltration of wandering cells. The elastica interna is clearly discernible. A completely organized thrombus which was fixed in the wall occupied the largest portion of the lumen. The thrombus showed abundant vascularization with vessels of different caliber of which some presented thick walls. The surface of the thrombus was coated with a thin elastic membrane which may have been due to a splitting of the internal elastica. The intima of the vessel did not show any proliferation. There was complete absence of the intima cushions which are specially characteristic of thrombo-angiitis obliterans. These characteristic alterations, however, may have been present in other portions of the vessel. The pathological alterations in Buerger's disease, as a matter of fact, show gross variations in the different cross sections of the vessel. This instance is also responsible for the different interpretations of the relation between the thrombi and the alterations of the vessel. Pictures as those described above suggest strongly primary thrombosis. Buerger himself believed that the disease was due to a primary thrombotic alteration; most likely he supported his view on pictures similar to those reported here. Frequently, however, gross alterations of the vessels, which must be considered primary, are found in Buerger's disease without presence of thrombotic formation."

The examination of the heart showed that the 2nd pulmonary sound was somewhat accentuated. The blood-pressure was 140 systolic and 100 diastolic. The roentgenogram and electrocardiogram of the heart showed nothing unusual.

The Wasserman reaction was negative for the blood. The sedimentation rate was 3 mm after 1 hour.

In the course of the three years which elapsed since the patient was discharged from the hospital, his condition with regard to the hemiparesis and the agraphia he had been exhibiting, was, as a whole, much the same. The spells of temporary blindness occurred gradually less frequently. In the early summer of the year 1938, the patient developed periodically severe pains in the left cheek and in the left half of the upper lip, which were preceded by fits of heavy sneezing.

*Summary:* Report of the history of a man, a joiner by profession, born in 1904. In the middle of June 1937, he had sudden, temporary seizures of agraphia. Towards the end of the month he became suddenly aphasic and developed hemiparesis of the right side. There was slow regression of those symptoms. In July there was recurrence of attacks of headaches on the left side. Since August he was subject to spells of blindness of the left eye. In October fits of aphasia set on, and he complained of his right arm feeling clumsy. This sensation subsided slowly. He was admitted to the hospital on January 1938. On admission he exhibited a slight hemiparesis with slightly increased reflexes in the right leg. The Babinski sign was negative on both sides. There was presence of positive Mendel-Bechterew signs on the right side. The arteriogram showed obliteration of the left carotid artery. Arteriography was performed on the right side and the contrast medium filled the anterior and medial cerebral arteries on both sides. The encephalogram revealed dilatation of the left lateral ventricle. In 1938 the patient developed pains in his left cheek. At the end of three years after discharge, the hemiparesis and the aphasia were unchanged. The spells of blindness occurred gradually less frequently. The findings at the pathological-anatomical examination suggested thrombo-angiitis obliterans, but did not definitely prove the presence of this condition.

*Case 8.* — Emerik T., born in 1895, contractor, a Fin, was treated at the Neurosurgical Clinic (Record 168/1939). There is nothing of interest in the family history of the patient. He had previously enjoyed good health. During the last year he manifested difficulty in breathing when ascending a hill or stairs. Since the spring of the year 1938, he had at times felt pains in the precordium accompanied by feelings of anxiety. In the autumn of the year 1938 he noticed that he dropped things which he held in his left hand. He gradually manifested increasing weakness and loss

of strength in his arm. Finally, there was hardly any motility left in the arm. There was also weakness of the left foot, although not so pronounced as in the left arm. Since the end of February he could not walk anymore, but was able to stand upright without any difficulty. Simultaneously a buzzing sound developed in his head, a kind of soft roaring which occurred synchronous with the pulse and he manifested also increasing difficulty in writing. Although he was left-handed, he used his right hand when writing. His hand-writing grew less and less legible, and shortly afterwards he exhibited difficulty in finding the proper words and letters. Apart from having at times had difficulty in finding the right words to express himself, he did not seem to have manifested any difficulty in speaking. On March 3, he was submitted to the Neurosurgical Clinic. On admission he manifested hemiparesis of the left side, most pronounced in the arm where there was hardly any motility left at all. The motility of the leg was fairly good, but its strength was reduced. There was presence of foot clonus on the left side. The Babinski sign was negative on both sides. The abdominal reflexes were normal. The patient further manifested a pronounced left-sided facial paresis of the central type and weakness to lift the shoulder on the left side. The tongue deviated to the left. Convergence was disturbed. The eyegrounds were normal. Slight hyperesthesia to touch was present in the left arm, but appreciation of pains and temperature was not impaired. Deep sensation was obviously reduced in the fingers and in the toes on the left side. Pronounced astereognosis was present in the left hand. His mental functions were not affected, but his arithmetical powers were poor. He was not able to do problems in addition with two figures, but numbers of one figure he cast up fairly well. His memory was not impaired. He manifested a pronounced agraphia. He was left-handed, but wrote with his right hand.

The roentgenogram of the skull did not reveal anything unusual.

Encephalographic examination revealed the following: absence of dislocation of the ventricular system. The left lateral ventricle showed dilatation, especially of the anterior part. Dilatation of the right lateral ventricle could not be definitely recognized. The position of the anterior and posterior portions of the third ventricle was normal. Somewhat widened sulci were visualized on the convexity.

The right common artery was arteriographically examined and the following was demonstrated: the contrast medium filled almost exclusively the external carotid artery. The roentgenogram which was taken four seconds after injection of the contrast medium showed that the contrast medium had entered the last portion of the siphone of the carotid artery and the vessels of the Sylvii group. The last mentioned vessels did not show any alterations. The wall of the siphone-areas of the carotid artery was somewhat irregular and suggested the presence of endarteritis.

Examination of the cerebrospinal fluid showed an inconsiderable admixture of blood. The Pandy test was negative. The blood count yielded the figure of 200 red and 4 white cells per 1 mm.

After the arteriographic examination the patient showed an obvious although slight amelioration of the paresis of the left arm.

Examination of the heart revealed nothing unusual. The blood-pressure was 150 systolic and 105 diastolic. The sedimentation rate was 7 mm after 1 hour.

He was discharged in the middle of the month with his condition unchanged. Two months later there was exacerbation of the paresis of the left leg. At that time he manifested symptoms suggestive of slight cardiac insufficiency and anginal pains. The patient died in his native country in June 1939.

*Summary:* Report of the history of a male, contractor by profession, born in 1895. Since the spring of the year 1938 he complained of pains in the precordium and sensations of anxiety. In the autumn of the same year he manifested increasing hemiparesis on the left side. Since February 1939 there was manifestation of aphasic symptoms and he complained of a roaring sound in his head. He was admitted to the hospital in March. On admission hemiparesis involving the left side was recognized. The Babinski sign was negative on both sides. On the left side there was presence of central facial paresis and of paresis of the accessorial and hypoglossal nerves. The left arm showed hyperesthesia and disturbance of deep sensation. Agraphia and alkalkulia were present. The patient was left-handed. The arteriogram showed alterations suggesting the presence of endarteritis in the siphone of the right carotid artery. The contrast medium was seen to fill the vessels of the Sylvii-group. Encephalographically it was recognized that the left lateral ventricle was dilated. At the end of two months after discharge there was exacerbation of the paresis of the left leg. The patient manifested symptoms suggestive of angina pectoris. Lethal exit occurred in June 1939.

*Case 9.* — *David K.*, workman, born in 1881, was submitted to the Neurosurgical Clinic (Record 525/1941). There was presence of ankylosis in the left knee following a trauma contracted as a child and in the joint of the right elbow since 1916 due to a tumour albus. Apart from these complaints, the patient had always enjoyed good health. In the beginning of April of the year 1941, he complained of numbness of the right hand. Shortly afterwards there was loss of power to recognize objects by touching or feeling them with his hands. At that time he manifested gradually difficulty in finding the proper name for the most common objects. These symptoms grew gradually worse. He began to stumble when walking and he complained of a «queer» sensation in his head. On April 23, his speech



grew more and more confused and he exhibited increasing difficulty in expressing himself. Finally his answers were confined to single words only. On April 25, he developed weakness of the right arm and a few days later also of the right leg. There was rapid impairment of the existent paresis which developed to paralysis. On May 2, he was submitted to the hospital of the district where he was resident. He appeared at that time very confused and showed an inclination to emotional outbursts. His consciousness was not disturbed. There was pronounced aphasia. He further exhibited a right-sided hemiparalysis. Appreciation of pin pricks was absent or grossly reduced on the right half of the body. Facial paresis of the inferior region was recognized. The muscular reflexes were normal. The Babinski sign was positive on the right side. The blood pressure was 220 systolic and 110 diastolic.

On August 22, he was admitted to the Neurosurgical Clinic. On admission he exhibited hemiparesis of the right side with inconsiderable motility still present in the arm and in the leg. The extremities showed normal muscular reflexes — as far as they could be tested. The Babinski sign was positive on the right side, the Trömner sign was negative on both sides. The abdominal reflexes were absent on the right side. The presence of facial paresis could not be definitely recognized. On attempts to lift his right shoulder, the patient displayed reduced strength. There was paralysis of ocular movement upwards. No further evidence of pathology with regard to the cranial nerves was recognized. The eyegrounds were normal. Superficial sensation was subjectively reduced on the entire right side, chiefly in the distal portion of the extremities. Deep sensation was reduced on the right side. The right hand showed astereognosis. There was presence of a pronounced aphasia, chiefly of the motor type.

The roentgenogram of the skull was normal.

Encephalographic examination revealed that the septum pellucidum as well as the third ventricle were situated in the median line. The right lateral ventricle was somewhat larger than the left, and its lateral superior cornu was somewhat disfigured laterally and upwards. Superior to the right frontal region, the sulci showed an enlarged volume and contained air in moderate quantities.

For the purpose of arteriographic examination the left common carotid artery and its branches were exposed. The common as well as the external carotid arteries were found to be normal, showing normal blood-pressure on palpation. In the bulbous a soft tumour of the size of a pea, not clearly demarcated, was palpable and superior to that area the internal carotid artery could be very easily compressed. The blood-pressure appeared to be normal, and the vessels appeared to be considerably narrower in that area than under normal conditions. The periphery of the vessel did not show any alterations. On injection of thorotrast into the common carotid artery it was observed that the contrast medium did not fill the internal carotid artery. On insertion of the needle through the reported tumour, good filling was obtained.

The roentgenographic examination showed the presence of irregularities of the wall and a slight obliteration of the lumen. The alterations measured 4 cm in length. The point of the needle penetrated as far as the inferior line of demarcation of this alteration. On injecting the contrast medium a large quantity took a retrograde course and filled the external carotid artery. The internal carotid artery was filled above the reported alteration. The siphone of the carotid artery was narrow and somewhat irregular. The anterior cerebral artery did not show any alterations, but the contrast medium did not enter the vessels of the Sylvii-group. The posterior cerebral artery was filled. The blood vessels filled with the contrast medium did not show any dislocation.

The physical examination revealed a hypertonia (230—120 mm) accompanied by a moderate enlargement of the heart, but otherwise nothing unusual.

The Wasserman test of the blood was negative. The sedimentation rate was 22 mm after 1 hour.

*Summary:* Report of the history of a workman born in 1881. In April 1941 he complained of his right hand feeling numb. This symptom grew gradually worse and was followed by weakness of the arm which developed to hemiparalysis. Simultaneously, there was development of a gradual increasing aphasia. The Babinski sign was positive on the right side. On the right side there was presence of paresis of the accessorius and hemianesthesia. Arteriographic examination showed an occlusion of the bulbus caroticus. The contrast medium did not fill the middle cerebral artery, but satisfactorily the anterior and posterior cerebral arteries. In the encephalogram it was seen that the right lateral ventricle was somewhat larger than the left.

The reported case-histories show that the incidence takes, to a certain extent, a characteristic course; most of the cases exhibit an initial stage present for different lengths of time in the course of which the cerebral symptoms set in periodically. There may, however, also be complete absence of this stage. The catastrophes are in the beginning generally of a mild character, abate rapidly, but increase in strength and duration subsequently. After a certain period which may cover several months or years, the symptoms following an attack reveal a more severe character than those preexisting. The final attack is at times of apoplectic character. It is, however, of more common occurrence that the catastrophes reach their full strength only after having gradually, during

the course of several hours, increased in intensity. The patients complain of dizziness, but are not unconscious. During the following days a slight abatement of the symptoms may be observed. Amelioration progresses very slowly, and after a short time the condition remains stationary. Frequently the individuals apply for treatment not until after this final severe attack.

The symptoms exhibited in thrombosis of the internal carotid artery have been described earlier by Moniz and other authors. On the basis of the cases that came under his own observation Moniz distinguishes a »syndrome of thrombosis of the internal carotid artery» which he describes as follows (see foot-note).<sup>1</sup> The symptoms which the authors cases manifested are rather well in agreement with Moniz's observations.

The object of the following report is to review the most important and most interesting symptoms associated with the incidence. For a closer study of the cases the reader is referred to the reported case-histories.

Frequently, the initial symptoms are headaches involving one side of the head and always localized on the same side as the thrombosed artery. Often, these headaches occur years before the manifestation of the other symptoms — as was the case in three of the nine cases that came under the author's own experience — sometimes at a later stage of the disease as it occurred in two of the author's cases.

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<sup>1</sup> Ces 4 malades, tous du sexe masculin, présentent une hémiparésie ou une hémiplegie du côté opposé à la thrombose de la carotide interne. Chez tous ces malades, même chez ceux qui ont présenté des troubles aphasiques graves et des hémiplegies très sévères, le facial n'a été que très légèrement touché.

C'est un fait à enregistrer; nous ne pouvons y trouver, pour le moment, une explication satisfaisante.

Parmi les symptômes prodromiques, nous citerons: les céphalées paraissent par crises, parfois longtemps avant les autres symptômes; des parasthésies fugaces aux membres; des crises souvent passagères, des parésies qui commencent plutôt par le membre supérieur; des convulsions qui ne sont jamais très intenses et qui surviennent parfois avec les troubles parétiques; parfois des troubles de sensibilité; crâne douloureux à la percussion, du côté de la thrombose; des troubles aphasiques (thrombose de la carotide interne gauche), ce que nous avons noté dans trois de nos quatre cas, constants et graves apparaissant par des crises passagères et toujours progressives, jusqu'à leur établissement définitif; ictus toujours très léger et très rapide, avec lequel survient en général une hémiplegie intense; du côté psychique, indifférence remarquable pour la maladie, parfois même une certaine euphorie. Nous noterons, que la palpation des artères carotides des deux côtés du cou ne donne pas des renseignements nets. En effet, la carotide externe accuse du côté malade, une pulsation assez forte.»

Neurasthenic symptoms, at times, are precursors of the onset of the disease.

The first coarse neurological symptom which is manifested is, as a rule, spastic hemiparesis involving chiefly the arm.<sup>1</sup> In the beginning the paresis is either of transient character (as was the case in three of the reported nine cases) and develops to a constant symptom, or (as was the case in five instances) it is right from the beginning irreversible. In some cases the paresis is at its onset but very weakly pronounced; the individual complains of a «sensation of clumsiness» in the paretical extremities.

Seven of the described cases exhibited a rather characteristic hemiparesis; in one case the spinally innervated musculature was unaffected and in one case both legs and one arm presented flaccid paresis.

All individuals exhibited facial paresis; in two cases — although the paresis was of central origin — the upper as well as the lower facial branch was involved.

In three cases hemianesthesia was definitely recognized.

The aphasic troubles, as a rule, set on subsequent to the manifestation of hemiparesis and are in the beginning usually of a transient character. In the six cases which manifested a left-sided alteration of the artery, there was evidence of aphasia. One case (case 5) was rather remarkable by reason of the presence of aphasic troubles in an individual who was right-handed and who presented arterial thrombosis on the right side and hemiparesis on the left side.<sup>2</sup>

In two cases (cases 7 and 8) there was manifestation of agraphia associated with poor arithmetical powers as an isolated asymbolic phenomenon.

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<sup>1</sup> Hemiplegia of this type in which the paresis is predominating in the upper extremity is reported by Foix and Lévy as being characteristic of vascular lesions within the cortical distribution area of the middle cerebral artery in opposition to proportional hemiplegia which is usually present if the central portion of the Sylvian-area is affected.

<sup>2</sup> A few cases of such a type are reported in the literature. Sörgo described one case and Siegert two. On of Siegert's cases (case 5) revealed at autopsy besides the presence of thrombosis of the right internal carotid artery and softening of the right hemisphere a severe sclerosis of the basal arteries of the brain. Riechert reported a case of internal carotid thrombosis associated with ipsilateral hemiparesis.

Among the symptoms of paroxysmal character which are less frequently present are parasthesias and pains in the heterolateral extremities.

In one case epileptic seizures occurred which were in the beginning of the Jackson type, but which gradually developed to grand mal.

Two of the described cases reported fits of sneezing; in one case (case 5) these fits occurred at the earliest stage of the disease, in the other case (case 7), not until the insults were persisting, in this case associated with pains in the cheek and in the upper lip, on the same side as the thrombosed artery. Antoni observed in a case of thromboangiitis obliterans in the brain accompanied by occlusion of the internal carotid artery similar, homolateral paresthesias in the cheek and the alveolar process.

Hyper- and hypaesthesia may occur in the region of the trigeminal nerve. Paresis of the hypoglossal nerve occurred in four of the cases, paresis of the accessorial nerve in three, both present on the opposite side of the thrombosed artery.

In one of the described cases a heterolateral pharyngeal paresis was recognized; in another case (case 6) a transient, homolateral, monocular visual impairment occurred, but apart from this instance, the eyes did not present anything unusual.

Not one of the cases that came under the author's own experience showed paralysis of the eye muscles. Siegert reported one case of homolateral paralysis of the abducens. Sörgo observed in a case paralysis of the rectus internus present on the same side as the thrombosed carotid artery and in six of eight cases there was presence of anisocoria with miosis on the side of the thrombosed artery.

Anisocoria of the same type was present in one of the described cases, but in this instance this condition was associated with thrombosis of the central retinal artery.

The eyegrounds were, with exception of two cases in which there was blurring of the borders of the disks, normal.

Paresis of vertical ocular movement upwards was present in one case (case 9) and presumably this condition was also present in another case (case 5), which on attempts to look up as well as to look down seemed to present paresis. In one case (case 8) paresis on convergency was recognized. Antoni reported a case in which there

the symptoms characteristic of thrombosis of the internal carotid artery. This trauma may have contributed to the development of thrombosis. Sorgo called attention to the relatively frequent occurrence of trauma of the skull in the past history of cases of thrombosis of the internal carotid artery.

Concerning the age of the individuals, that is to say, the age at which the cerebral symptoms became apparent, the following is to be reported. One individual was in the third decade at the onset of the disease, three were in the fourth, four in the fifth and one in the seventh decade. Two of the cases were females.

The physique of all individuals was normal, they were well nourished and showed normal musculature. In one case nevi pigmentosi were observed showing a tendency towards radicular expansion, an instance which is rather interesting as it concurs with Moniz' observation of a nevus vasculosus showing a similar expansion.

Increase in blood-pressure was observed in three cases. Determinations during the hospitalization time of these patients in the Serafimer hospital, Stockholm, yielded systolic the highest values of 230, 195 and 180 mm Hg, respectively.

It is a known fact that a sudden drop of the blood-pressure causes at times cerebral symptoms such as hemiparesis, aphasia, a. s. o. (Cobb, Tournay). Not one of the cases reported in this paper manifested gross fluctuations with regard to the blood-pressure and their history did not contain any data indicative of such either; consequently there is no definite evidence available in support of the assumption that the same kind of symptoms which occur in thrombosis of the internal carotid artery, are due to a general drop of the blood-pressure.

The clinical examination of the heart of all cases did not reveal any unusual alterations. The electrocardiogram of one case revealed signs suggestive of intraventricular conduction block and right ventricular preponderance. In the roentgenomgram of this case there was also evidence of enlargement of the heart. The heart of the majority of the patients was electrocardiographically and roentgenologically examined and showed only exceptionally pathological alterations which, if present at all, were inconsiderable.

In two cases the arteries of the extremities were roentgenologically examined and in one of these cases the presence of a slight

calcification of the wall of the arteries of the inferior part of the leg was recognized. Oscillometric examination of the extremities was carried out in two cases and revealed the presence of pathological conditions in one case (case 4). Apart from the reported findings nothing unusual was found on examination of the vascular system. The other inner organs appeared to be unaffected.

With exception of two cases the cerebrospinal fluid was found to be normal. In one of these cases the mastic test yielded a curve suggestive of pathological alterations and in the other case there was an increase in the number of cells. The blood and urine tests yielded in all cases normal values. The Wasserman reaction and other serological tests for lues were in all cases negative.

In all cases diagnosis was established by means of arteriographical examination of the artery. For this purpose the internal or common carotid arteries were exposed and thorotrast injected. In eight cases a passage-hindrance was recognized; in seven of these cases the inferior line of demarcation of the occlusion was found to be at the point where the internal carotid artery branches off from the common carotid artery or one or two centimeters superior to that point; in one instance the occlusion was localized in the siphone of the carotid artery. In one case there was presence of endarteritis in the siphone without occlusion. In six cases an alteration of the artery was found localized on the left side, in three cases it was present on the right side.

In one case the internal carotid arteries of both sides were arteriographically examined. In this instance the anterior and middle cerebral arteries within both hemispheres were filled by way of the functioning artery. It results therefrom that in this case the circle of Willis was to a certain extent able to compensate the inhibited function of one of the internal carotid arteries. The cerebral symptoms were also in this case relatively mildly pronounced. This instance is in full agreement with Moniz' and Krieg's observations. Contrary to Krieg's statement that, as a rule, there is regression of the deficiency symptoms in such cases, the cases in question did not show any clinical amelioration; at the end of three years after the onset of the catastrophes, hemiparesis and aphasia had not changed.

Six cases were encephalographically examined. In three cases a widening of the lateral ventricle on the same side as the damaged

carotid artery was demonstrated, in two cases this condition was found in association with an increase in air present in the sulci of the convexity. In one of these cases there was further displacement of the ventricular system towards the side of the affected artery. In one case the lateral ventricle on the opposite side of the thrombosed internal carotid artery was wider than that of the homolateral side; in one case it was definitely proved to be dilated.

Reviewing the literature the author found twenty three cases reported in which diagnosis had been established during life by means of arteriographic examination.

Three of the cases were at the onset of the disease in the third decade, two in the fourth, eight in the fifth, nine in the sixth and one in the seventh. Among these cases there were only four females. The coarse neurological symptoms seemed to have set on acutely in about half the cases; in one third of the cases the disease took a chronic-progressive course. As some of the cases published in the literature are not exhaustively described, it is not possible to give exact values with regard to this question.

In ten cases the manifestation of premonitory attacks of headaches were reported, in two of these cases coexisting with diplopia. Six cases manifested of the usual initial symptoms of transient character hemiparesis, two hemiparesthesia and one case paresthesias in the contralateral arm. Transient aphasic symptoms were described in three cases; in two of these cases these symptoms were associated with transient hemiparesis, in the third there was coexistence of a left-sided facial paresis with occlusion of the internal carotid artery on the right side. (Whether this patient had been left-handed, is not reported).

Of the persisting cerebral symptoms hemiparesis was present in seventeen cases, in one case there was presence of monoplegia involving the arm and in one case involving the leg. In four cases there was absence of spinal motoric symptoms. The presence of facial paresis was reported in twelve cases. In one case paresis of the abducens was observed, in one case paresis of the internal rectus muscle, in both cases on the same side as the thrombosed artery.

Sorgo reported that six of eight cases exhibited anisocoria associated with miosis of the pupil on the same side as the thrombosed artery, and Siegert stated that these conditions were present in one



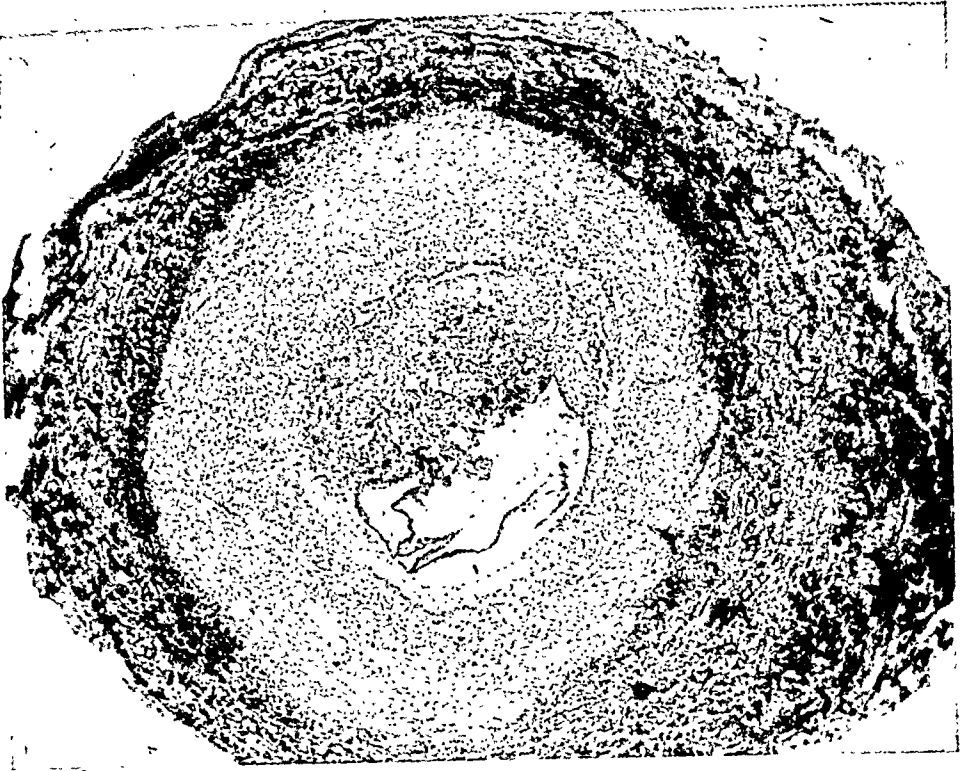


Fig. 1. (Case 1. —) Cross section of the left internal carotid artery showing thrombosis, 22 times enlarged. Staining: Hematoxylin-Eosin.

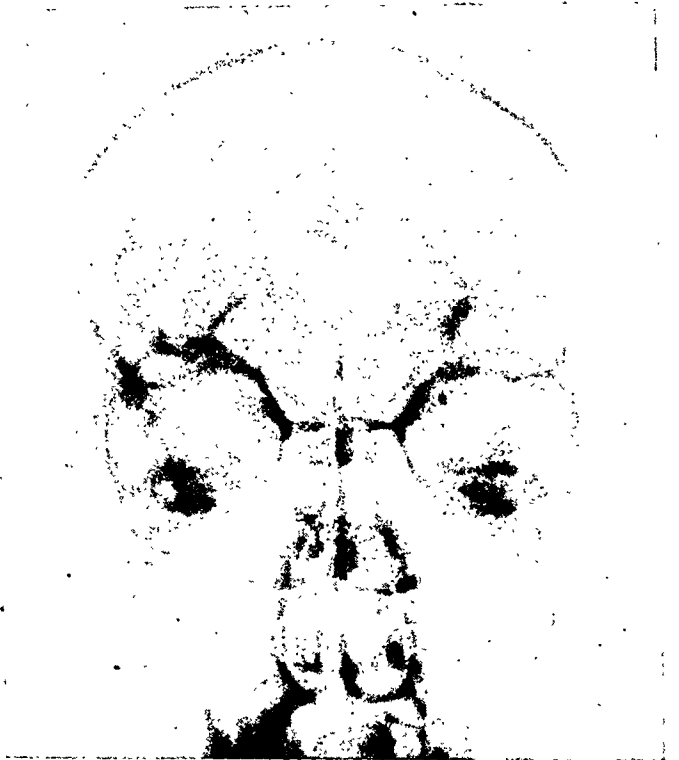


Fig. 2. Case 7. Encephalogram. Dilatation of the left lateral ventricle.



Figs. 3 and 4. Case 7. Arteriography of the right carotid artery. The contrast medium fills the anterior and middle cerebral arteries on both sides.

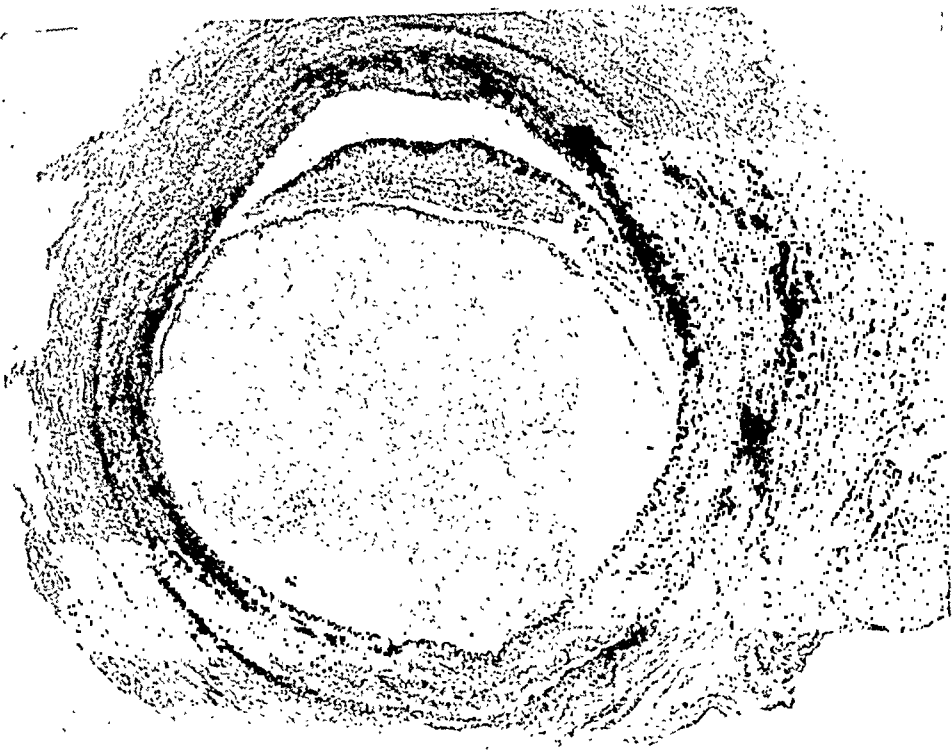


Fig. 5. Case 7. Cross section of the left internal carotid artery showing thrombosis, 22 times enlarged. Staining: Weigert's hematoxylin v. Gieson.

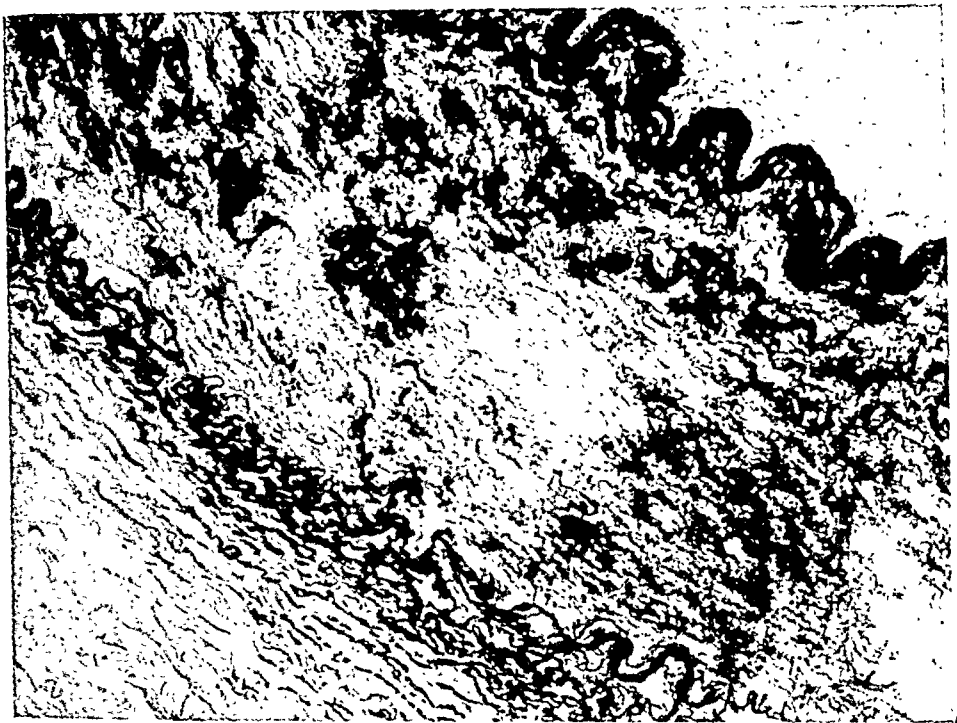


Fig. 6. Case 7. Left internal carotid artery. In some areas of the media the elastic substance is increased, in others there is a decrease. 110 times enlarged. Elastin-staining.

of the two cases that came under his observation. Alterations of the eyegrounds suggestive of a mild stasis were occasionally observed (Riechert, Sorgo). Moniz reported the presence of a pronounced papillary stasis in one case.

Of the twenty three cases published in the literature the arterial thrombosis was localized on the left side in sixteen cases. In thirteen of these cases persistent aphasic disturbances were observed. In one case the presence of aphasia was reported associated with thrombosis of the right internal carotid artery; the respective patient was right-handed.

Gradual amelioration of the symptoms occurred in about half the cases, in two cases after excision of a segment of the thrombosed internal carotid artery. Death occurred in five cases. In two of these due to intercurrent diseases.

On exposing the internal carotid artery the diameter of the damaged artery was found to be grossly reduced in some of the cases that came under the author's observation. In two cases (case 1 and 7) a segment of the thrombosed artery was excised and subjected to pathological-anatomical examination. In one case the presence of an inflammatory cell infiltration in the thrombosed artery was demonstrated. Presumably this lesion was due to arteriosclerosis. In the other case there was evidence of an increased quantity of collagenic substance in the adventitia, further it was found that the elastic substance present in the media showed an increase in some areas of the cross section whereas in other areas the substance was reduced. Besides there was presence of inconsiderable cell infiltration within the adventitia and media. In this case one was entitled to the assumption that the alterations were due to thrombo-angiitis obliterans.

In one case (case 3) the brain had been examined and described earlier by Antoni who found alterations of the cerebral arteries due to thrombo-angiitis obliterans whereas no definite evidence could be established that the lesions of the internal carotid artery were also to be attributed to thrombo-angiitis obliterans.

Of the cases of thrombosis of the internal carotid artery diagnosed by means of arteriography and reported in the literature, the author found five cases in which pathological-anatomical examination of the damaged artery had been made. Sorgo described two

cases. In one case there was presence of thrombo-angiitis obliterans in association with occlusion of the internal carotid artery due to arteriosclerosis; in the other case the carotids were severely damaged owing to arteriosclerotic alterations. Sörgo advanced the view that most likely all cases of thrombosis of the internal carotid artery are due to arteriosclerotic processes. Ricchert reported arteriosclerotic alterations of the thrombosed artery in one of the cases that came under his own observation. Chao and collaborators described two cases in which organized thromboses localized in the internal carotid artery were demonstrated. These authors did not state anything about the nature of the alterations. The other seventeen cases reported in the literature were not subjected to pathological-anatomical examination. In seven of these cases the diagnosis arteriosclerosis was assumed to be correct. Apart from the cases of thrombo-angiitis obliterans referred to previously in which the correctness of the diagnosis was histologically proved, Sörgo suspected in one case the presence of thrombo-angiitis obliterans. In another case studied by Sörgo, Schüller-Christian's disease occurred subsequently.<sup>1</sup> One of Moniz' cases manifested lues which had given cerebrospinal symptoms at an earlier period already. In the remaining seven cases nothing was detected which might have helped towards throwing some light on the nature of the alterations of the blood vessel.

Antoni described two more cases in which there was presence of thrombo-angiitis obliterans of the cerebral arteries associated with thrombosis of the internal carotid artery, and in which the alterations in the carotid were recognized to be sclerotic.

Most likely arteriosclerosis is in the majority of the cases responsible for thrombosis of the internal carotid artery. Doerfler and other authors have demonstrated that arteriosclerosis of the internal carotid artery — frequently limited to that artery — is of common occurrence and that it may appear already during youth. Hultquist published recently his studies of a material covering about 3,500 cases on which post-mortem examination was performed at the St. Erik's Hospital in Stockholm. In ninety-one of the cases (2.6 %) thrombo-embolic alterations were found in the

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<sup>1</sup> Hultquist described a case of Schüller-Christian's disease in which the coexistence of thrombosis of the internal carotid artery was found at autopsy.

internal and common carotid arteries. In sixty-nine cases these alterations could be macroscopically visualized, in twenty-two cases they only could be demonstrated in the microscope. Hultquist stated that in all cases of primary thrombosis that came under his observation, the alterations were of the arteriosclerotic type.

In one of the authors own cases (case 3) the brain was examined by Antoni who reported his findings on an earlier occasion. The internal carotid artery and the middle cerebral artery were found to be occluded on the left side, and the latter artery showed alterations characteristic of thrombo-angiitis obliterans. Within the left parietal lobe there was presence of malacic foci in the cortex and in the white matter lying underneath it. Attention should be called to the fact that the clinical picture of the disease in this instance is of special character and completely different from that usually observed in cases of thrombosis of the internal carotid artery and from the picture which the other cases that came under the author's observation, exhibited.

Antoni reported two more cases of cerebral thrombo-angiitis obliterans with thrombosis of the internal carotid artery of which one case presented occlusion of the left carotid artery associated with malacic alterations chiefly of the cortical- and marrow layer of the inferior frontal gyrus anterior to Broca's zone and to the left middle frontal gyrus; in the other case presenting occlusion of the right carotid artery there was presence of a softening focus within the right hemisphere in the parietal region and in the posterior frontal region extending deep into the marrow as well as of small malacias in the temporal lobe. Within the left hemisphere the cortex seemed to be intact. In both cases alterations in the central ganglions were found.

Sorgo described a case of occlusion of the left internal carotid artery in association with cerebral thrombo-angiitis obliterans. In the brain there was presence of extensive softening of almost the entire layer of the marrow of the left hemisphere as well as of foci in the right hemisphere. In one more case that came under Sorgo's observation a rather severe atrophy of the hemisphere of the same side as the occlusion involving chiefly the base of the second and third frontal gyrus within the boundary area between the anterior and middle cerebral arteries and extending to the base of the

frontal brain was found. In these cortical areas there was presence of malacia. The right hemisphere exhibited »Hirnschwellung» and malacic alterations which were not very strongly pronounced.

Lindenberg and Spatz were responsible for the pathological-anatomical examination of 20 cases of thrombo-angiitis obliterans of the cerebral vessels. With regard of the site of the lesions, these authors differentiated two different main types: (1) in six of the cases extensive malacias were demonstrated within the distribution area of one or several of the large arteries, which were chiefly limited to one of the two hemispheres and which were predominantly localized in the cortical area. These severe cerebral lesions in association with peripheral circulatory disturbances occurring at times in this type of cases, made the establishment of a clinical diagnosis in some cases possible; (2) in fourteen cases there was presence of lesions of the type »granuläre Atrophie der Grosshirnrinde» localized in the border area between the three large arteries of the brain, the distal portions of which — and exclusively these — presented alterations as seen in thrombo-angiitis obliterans. These lesions occurred in both hemispheres and showed symmetrical extension. In some cases of the two reported, types there was thrombosis of the internal carotid artery besides, the alterations referred to above.

Brain lesions occurring subsequent to ligature of the internal or common carotid arteries performed for therapeutic purposes, are mostly localized in the distribution area of the middle cerebral artery.

Müller studied two cases in which ligature of the carotid artery was performed and one case of arterial embolus. This author observed that within the involved cortical area unaffected areas seemed to be irregularly disseminated. As these intact cortical areas frequently are localized right in the middle of the area which is supplied by the middle cerebral artery, Müller was of opinion that one has to rule out the concept of a collateral circulation as explanation, and advanced the view that the qualities of the tissue in itself should be considered to give rise to the more or less strongly pronounced lesions.

Döring observed in one case in which ligature of the common artery was performed, within the right hemisphere necrosis of the distribution area of the middle cerebral artery and — an instance

which is rather remarkable — within the left cortical hemisphere, small, spot-like lesions.

Cammermeyer found in one case subsequent to ligature of the internal carotid artery on the same side »considerable necrosis of the cortical area supplied by the end branches of the middle cerebral artery» involving exclusively the cortical area and not encroaching the white substance nor the basal ganglions. The author interprets these lesions as after-effects of an embolus.

According to Hultquist whose pathological-anatomical examinations of alterations of the brain in the presence of carotid thrombo-embolism cover a very large material, the lesions occur preferably within the area of the middle cerebral artery and are most strongly pronounced in the anterior central parts of this area. In about half the cases which Hultquist studied there was presence of diffuse alterations of the areas supplied by the anterior and posterior cerebral arteries. In some cases Hultquist observed alterations in the form of foci in the contralateral hemisphere — especially in the outmost cortical layer — localised in the distribution areas of the middle as well as of the anterior and posterior cerebral arteries. Hultquist emphasized that the cerebral alterations present in thrombo-embolism of the carotid artery are always stronger pronounced in the cortex and in the subcortical area.

For some time one has been suspecting that in cases of embolism or arteritis of the cerebral arteries, vaso-constrictive spasms<sup>1</sup> are contributing to the development of cerebral lesions. Moniz and

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<sup>1</sup> A number of experimental examinations undertaken for the purpose of throwing some light on the innervation conditions of the cerebral arteries have yielded contradictory results. The results obtained by Putnam and Ask-Upmark, Schneider, Bouckaert and Jourdan, Gollwitzer-Meier and Eckardt suggest a vaso-constrictive action of the sympathicus on the cerebral arteries. Irritation of the sympathicus is supposed to cause constriction of the arteries of the homolateral hemisphere as well as of those of the heterolateral hemisphere.

According to the results of the examinations carried out by Ask-Upmark and Bouckaert and Jourdan the presso-receptive zone in the carotid sinus is supposed to have an effect on the tonus of the cerebral arteries, not only indirectly by way of the general blood-pressure, but most likely also directly, whereby in the latter case, the cerebral arteries, in the presence of a decrease in pressure in the sinus, respond with a vaso-constriction.

Fog, however, stated that the tonus of the cerebral arteries certainly is influenced by the blood-pressure, but there is as yet no evidence established that a neurogenic-constrictive stimulus is exercised on the cerebral arteries. (For further information about the respective literature see Ask-Upmark and Schneider).



other authors presumed that the transient neurological symptoms in thrombosis of the internal carotid artery characterizing the initial stage of this accident, are due to spasms in the cerebral arteries caused by reflex-action.

It may be that the irreversible symptoms which appear at a later stage in the course of the disease, find their explanation based on this supposition. As a matter of fact, it is still obscure at what date eventual occlusion of the damaged internal carotid artery actually occurs. That the occlusion coincides with the persisting cerebral symptoms is by no means definitely proved.

The concept that vaso-constrictive phenomena play a part in the development of the symptom-complex of thrombosis of the internal carotid artery furnishes a feasible explanation of several symptoms manifested in this incidence which are otherwise rather obscure.

1) Even incomplete occlusion of the internal carotid artery is sometimes giving rise to the typical clinical picture characterizing the disease. In one of the reported cases (case 8) there was presence of endarteritis of the internal carotid artery associated with only a moderate occlusion of the lumen. In this patient the picture of the disease was in full agreement with the picture characteristic of thrombosis of the internal carotid artery; one might, however, say that the disease progressed more insidiously than was usually the case. Sorgo described two cases of this type. Moniz observed similar cases: »We also saw incomplete thromboses and other forms of partial occlusion of the internal carotid artery in which the picture of the disease was the same as that seen in complete occlusion.»

2) Symptoms indicative of lesions localized in the heterolateral hemisphere occurred: in one case (case 5) there was presence of a motor aphasia associated with a thrombosis of the right internal carotid artery in a right-handed individual. The aphasia was in the beginning of the usual intermittent character and a thrombosis of the left middle cerebral artery does not seem very probable. No symptoms were present in this case which might have suggested cerebral thrombo-angiitis obliterans. If one departs from the assumption that the speech-centers are localized on the left side, the above described conditions can hardly be explained by the assumption that thrombosis of the right internal carotid artery,

exclusively by mechanical occlusion of the artery which causes impairment of the cerebral blood-supply, gives rise to cerebral lesions in the *arteria Sylvica*-area on the opposite side of the blocked artery. A feasible explanation of this phenomenon however can, be furnished on the basis of the assumption that spasms in the cerebral arteries are elicited from the damaged internal carotid artery by reflex-action.

The chief object of the therapeutic treatment of thrombosis of the internal carotid artery should be the prevention of the occurrence of cerebral lesions by maintaining an adequate blood-supply of the brain. The hypothesis that the cerebral ischemia in thrombosis of the internal carotid artery is due chiefly to spasms in the cerebral arteries elicited from the damaged carotid artery, appears to be rather attractive. It results therefrom that excision of the damaged segment of the artery (after Leriche's method) seems to be advisable in some cases.

Even at the stage of the disease when the neurological symptoms are still of transient character, the picture of the disease — as stated by Moniz — should be sufficiently characteristic, especially on account of its intermittent course — to allow the supposition of the correct diagnosis. Evidence may be established by means of arteriographic examination.

Several cases are reported in which resection of the thrombosed segment of the artery was performed; in all cases surgical intervention was made at a late stage of the disease. Chao, Kwan, Lyman & Loucks observed in two cases which manifested coarse neurological symptoms as a sequence of the surgical intervention improvement of mental performance. Riechert reported an amelioration following surgical intervention in two cases of which one manifested regression of hemiparesis and improvement of mental functions. The other case was as a sequence of the operation free from the central pains existing previously.

Of the cases studied by the author, resection of the thrombosed segment of the internal carotid artery was performed in two cases, although unfortunately only partially. Not one of these cases showed definite amelioration.

As the possibilities of restitution of the damaged tissue of the brain are limited, the surgical intervention should be performed at the earliest stage of the incidence.

## Summary.

Nine cases of thrombosis of the internal carotid artery are described. In all cases diagnosis was established by means of arteriography during life.

The author gives a review of the respective reports in the literature.

The course of the disease is, to a certain extent, characteristic. The cerebral deficiency symptoms are in the beginning of transient character, but become gradually persisting and are due to alterations in the distribution area of the middle cerebral artery and — although less frequently — of the ophthalmic artery.

The author emphasizes that the obliteration of the artery caused by thrombosis and the decrease in the blood supply of the brain associated with this condition, cannot alone, in and for themselves, give rise to the cerebral lesions. In support of this concept the author states that sometimes only the contralateral hemisphere is giving symptoms, further, that a completely developed symptom-complex may be observed in endarteritis of arteries presenting only an inconsiderable decrease of caliber, and finally the author refers to the observations made by other authors at post-mortem examinations.

According to the author, it is most likely that the cerebral lesions in thrombosis of the internal carotid artery are, to a large extent, due to spasms of the cerebral arteries caused by reflex-action and elicited by the damaged carotid artery.

I wish to express my grateful appreciation to Professor Nils Antoni for having animated me to write this paper. I am indebted to him for valuable aid and guidance.

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## Über den Glykogengehalt des Blutes

von

PEKKA BRUMMER.

(Bei der Redaktion am 22. März 1943 eingegangen).

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### *Über die Bestimmungsmethoden.*

In den meisten im Schrifttum erschienenen Untersuchungen über den Glykogengehalt des Blutes ist die Glykogenbestimmung entweder nach der ursprünglichen Pflüger'schen Methode oder einer ihrer Modifikationen ausgeführt worden. Bei allen diesen gilt als wesentliches Prinzip, dass das Blut erst mit starkem Kaliumhydroxyd hydrolysiert, aus dem Hydrolysegemisch Glykogen mit Alkohol ausgefällt und dann meistens zu Glykose zersetzt bestimmt wird.

Bei Beurteilung der mittels der Pflügerschen Methode gewonnenen Ergebnisse ist zu berücksichtigen, dass das Glykogen keineswegs das einzige mit Alkohol auszufällende, gegen Alkalihydrolyse resistente Kohlehydrat ist, sondern dass diese Eigenschaften den Polysacchariden schon von den Trisacchariden an gemeinsam sind (z. B. v. Lippmann). Wenn man also annehmen kann, ein zu untersuchendes Gewebe enthalte einige andere Polysaccharide als Glykogen, so werden sie bei Anwendung der Pflügerschen Methode mit bestimmt. Ein derartiges Polysaccharid ist denn auch nach den neuesten Untersuchungen im Kohlehydratkomponente der Eiweisskörper anzutreffen. Levene und seine Mitarbeiter, Rimington, Blix und Sörensen, haben nämlich erwiesen, dass der Kohlehydratteil besonders der Glykoproteide, aber auch wahrscheinlich anderer Eiweisskörper wenigstens teilweise Trisaccharid ist. In dieselbe Richtung weist die schon von Bywaters seinerzeit gemachte Beobachtung, dass das in den Glykoproteiden anzutreffende Kohlehydrat nur zum Teil bei Alkalihydrolyse zersetzt wird.

Um die oben dargestellten Annahmen zu bestätigen, habe ich teils mit reinen Industrie-Eiweisspräparaten (Albumin aus Ei und Albumin aus Blut,

Schering-Kahlbaum), teils mit mehrmals ausgefällten Serumproteinen Versuche ausgeführt. Trotz mehrstündiger Hydrolyse mit 60 %iger KOH-Lösung ist bei allen diesen Versuchen stets ein mit Alkohol ausfällbarer, nach Säurehydrolyse reduzierender Rest übriggeblieben, dessen Menge, als Glykose angegeben, auf 0.1—0.2 % von der Menge des Eiweisskörpers gestiegen ist.

*Durch diese Versuche ist meines Erachtens bindend erwiesen, dass die auf Pflüger'sche Verfahren gegründeten Bestimmungsmethoden unbrauchbar sind zum mindesten bei der Bestimmung des Glykogens aus dem Blut, in dem einerseits der Glykogengehalt niedrig und anderseits die Menge des Eiweisses und wenigstens teilweise sein Kohlehydratgehalt (die Glykoproteide des Blutes) verhältnismässig hoch sind, soweit man den Begriff Glykogen nicht ganz neuzufassen gedenkt, indem man unter ihm, wie Goländas es getan hat, einen der Alkalihydrolyse widerstehenden Substanz versteht, der ausdrücklich nach der Pflügerschen Methode aus Blut ausgefällt ist.*

Auf Grund des oben Dargestellten sind die verhältnismässig hohen Glykogenwerte zu verstehen, die man mit der Pflügerschen Methode für Blut erhalten hat und die bei den verschiedenen Verfassern von 10 bis 40 mg % und noch höher geschwankt haben.

Ein anderer Weg bei der Untersuchung des Glykogengehalts besteht darin, dass man statt der Hydrolyse zunächst die Eiweisskörper ausfällt und das Glykogen aus den Filtrat bestimmt. Die einzige eigentliche auf dieses Prinzip gegründete Mikromethode ist die von de Jongh und Planelles, bei der das Blut durch Trichloressigsäure enteiwisst wird, aus dem Filtrat das Glykogen durch Alkohol-Äthergemisch ausgefällt und dadurch bestimmt wird, dass man die Intensität der so entstandenen Trübung mit einer fertigen Verdünnungsserie vergleicht.

Bei meiner Methode, die sich auf die oben dargestellte gründet, wird das Blut ebenfalls durch Trichloressigsäure enteiwisst; danach setzt man zu einem Teil Filtrat 2 Teile 96 %igen Alkohol und bestimmt nephelometrisch die Intensität der Trübung. Das aus trichloressigsaurer Lösung mit Alkohol ausgefällte Glykogen bildet eine besonders haltbare Trübung; zur Stabilisierung ihrer Haltbarkeit habe ich ihr noch etwas Digitonin zugesetzt. Die Anwesenheit von Digitonin ist ferner dazu geeignet, die Hämolyse der Blutprobe vor dem Enteiwissen zu begünstigen und dadurch die Gefahr dass das in den Blutzellen enthaltene Glykogen mit den Eiweisskörpern ausgefällt werden könnte, zu verringern. Die Verwendung von Alkohol-Äthergemisch bei der Ausfällung des Glykogens ist nicht notwendig, weil einerseits das Glykogen in dem benutzten 60 %igen Alkoholgehalt quantitativ ausgefällt wird und da anderseits der Äther andere, nicht zur Sache gehörige Stoffe ausfällen kann.

Die Methode ist im einzelnen folgende:

Die erforderlichen Lösungen:

50 mg %ige Digitoninwasserlösung

30 %ige Trichloressigsäurelösung

96 %iger Alkohol.

Ausführung:

In 2 ml Zitratblut werden 3 ml Digitoninlösung sowie nach einigen Minuten 1 ml Trichloressigsäure gegeben, danach wird zentrifugiert und filtriert. 2 ml Filtrat setzt man 4 ml Alkohol zu und nephelometriert nach 15 Minuten. Das Nephelometrieren habe ich mit dem Duposcq'schen Kolorimeter ausgeführt.

Die zu untersuchende Blutprobe muss unmittelbar vor der Bestimmung genommen werden, da im Blut, wenn es steht, verhältnismässig schnell Glykogenolyse eintreten kann; dagegen kann die Probe nach Hinzuführung von Trichloressigsäure gut viele Stunden stehen, ohne dass irgendeine Schwund von Glykogen eintritt.

Als Fehlergrenze der Methode stellte sich  $\pm 5-10\%$  heraus, welcher Betrag als völlig befriedigend gelten kann.

Bestimmt man das Glykogen auf die oben dargestellte Weise, so wird wenigstens das freie Glykogen nicht mit den Eiweisskörpern ausgefällt, denn einerseits zeigte es sich, dass das Glykogen in Trichloressigsäure leichter als in Wasser löslich war, und andererseits lässt sich das dem Blut zugesetzte Glykogen durch meine Methode quantitativ zurückgewinnen.

Eine Fehlermöglichkeit bei meinem Verfahren besteht darin, dass das Blut vielleicht andere Bestandteile als Glykogen enthält, die nicht beim Enteiweissen wohl aber mit 60 %igem Alkohol ausgefällt werden. In Versuchen, die ich in dieser Hinsicht mit den verschiedenen normalen Bestandteilen des Blutes angestellt habe, ist jedoch kein Stoff anzutreffen gewesen, der unter diesen Verhältnissen wenigstens in dem Gehalt, mit dem er im Blut vorkommt, ausgefällt worden wäre oder der sonstwie auf die Stärke der Glykogentrübung eingewirkt hätte. In Krankheitsfällen ist das nicht ebenso sicher. So ist zu bemerken, dass das Filtrat aus dem Blut vorwiegend von Patienten mit Infektionskrankheiten nach Ausfällung mit Trichloressigsäure nicht immer ganz klar wird. Es erwies sich, dass die Stärke dieser Trübung vom Trichloressigsäuregehalt stark abhängig war. Obgleich die Trübung sich in Alkohol aufzulösen und die Grösse der erhaltenen Werte von der Stärke dieser Trübung unabhängig zu sein schien, schliesst dennoch ihr Vorhandensein eine Fehlermöglichkeit ein.

Als Zusammenfassung der Besprechung etwaiger Fehlerquellen der Methode kann festgestellt werden, dass die Ergebnisse im übrigen zuverlässig sind, abgesehen davon, dass man über die in Krankheitsfällen konstatierten gesteigerten Werte nicht mit voller Sicherheit aussagen kann, ob sie wirklich auf dem vermehrten Glykogengehalt oder auf irgendeinem pathologischen Bestandteil des Blutes beruhen.

*Die klinischen Ergebnisse.*

Nach den früher im Schrifttum dargestellten Angaben folgen die im Glykogengehalt des Blutes festgestellten Veränderungen im grossen ganzen den Schwankungen des Blutzuckers. So behauptet man, Zuckerbelastung und Adrenalin bewirkten gesteigerte und Insulin herabgesetzte



Werte sowie Störungen im Glykogengehalt des Blutes träten bei Diabetes und ferner bei Leberkrankheiten auf (z. B. London und Entin, Weinstein und Schatalowa, Staub und Golandas, Sikinami, Hosokowa und Oba). Da jedoch diese Ergebnisse durch verschiedene auf Pflügers Methode gegründete Bestimmungsmethoden erlangt worden sind, kann man ihnen bei der Beurteilung des Glykogengehalts im Blut keine nennenswerte Bedeutung zusprechen, weswegen ich in diesem Zusammenhang nicht ausführlicher auf sie eingehe.

Schwarz und Gerson, die die Methode von de Jongh und Planelles angewandt haben, erwähnen, der normale Glykogengehalt des Blutes sei etwa 1: 100 000, also bedeutend niedriger als die obengenannten mit Pflügers Methode erhaltenen Werte. Auch die übrigen Forscher, die statt Anwendung von Alkalihydrolyse die Eiweisskörper ausgefällt haben, sind desgleichen zu 1—2 mg % Glykogengehalt des Blutes gekommen (z. B. Huppert), unabhängig davon, wie die endgültige Glykogenbestimmung ausgeführt worden ist.

In pathologischen Fällen begegneten Schwarz und Gerson besonders im Zusammenhang mit Diabetes, schweren Leberkrankheiten und bösartigen Geschwulsten gesteigerten Werten; der Glykogengehalt konnte dabei bis auf einen Wert von 1: 2000 steigen; ausserdem führen sie an, in einem Lungenentzündungsfall einen hohen Wert erhalten zu haben.

Ich selbst habe an klinischem Material in 125 Fällen Glykogenbestimmungen ausgeführt. Die Bestimmungen sind ausschliesslich an Blut, nicht an Serum angestellt worden, und die Proben hat man morgens bei leerem Magen entnommen.

Das Material umfasste 30 Gesunde oder ihnen Vergleichbare. Bei ihnen allen wechselte der Glykogengehalt des Blutes von 1—3 mg%.

Entgegen den früheren Kenntnissen waren im Zusammenhang mit dem Diabetes keine nennenswerten Veränderungen im Glykogengehalt festzustellen. Das Material enthielt 12 Diabetesfälle, von denen der grösste Teil aus schweren oder mittelschweren bestand. Bei 10 von ihnen war der Glykogengehalt des Blutes selbst bei fortgesetzten Untersuchungen ganz normal und nur in 2 etwas gestiegen, nämlich auf 4 mg % und 5 mg %, trotzdem der Blutzucker gleichzeitig beträchtlich hoch, ja über 300 mg %, sein konnte. Bei Zuckerbelastung, in 5 Fällen von mir ausgeführt, konnten in den Glykogenwerten keine Veränderungen festgestellt werden, ebensowenig liess Insulin irgendeinen Einfluss erkennen. Auf Grund dieser Ergebnisse ist es offenbar, dass dem Glykogen des Blutes im Kohlenhydratstoffwechsel keine nennenswerte Bedeutung zukommt.

Normale Werte traten ferner in allen 10 untersuchten Herzinsuffizienzfällen auf, trotzdem sie schwerer Art waren, desgleichen in allen Koronarthrombose-, Nephritis- und Ulkusfällen. Auch der Glykogengehalt dreier zum Material gehörenden graviden Frauen war normal, ebenso auch der eines an schwerer Muskeldystrophie erkrankten Patienten.

An Leberkrankheiten umfasste das Material ausser den 10 obengenannten Herzinsuffizienzfällen, in denen allen es sich um eine ausgesprochene Stauungsleber handelte, insgesamt 6, von denen 4 akute Hepatitis und 2 Zirrhose waren. Bei ihnen allen waren die Glykogenwerte normal.

Unter verschiedenen Krebsfällen war bei 12 Fällen der Glykogengehalt normal und nur bei 4 etwas gestiegen; der höchste festgestellte Wert war 15 mg %. Alle Fälle, in denen gesteigerte Werte festgestellt werden konnten, waren in hohem Masse kachektisch, so dass die Veränderungen im Glykogengehalt des Blutes offenbar bei Krebskrankheiten in keiner Weise zum Krankheitsbild gehören.

Die grössten festgestellten Veränderungen traten in meinem Material im Zusammenhang mit Lungenentzündung auf. So belief sich der Glykogengehalt bei 6 katarrhalischen Pneumonie auf 7, 8, 9, 10, 12 und 15 mg % und bei 15 Fällen von lobärer Pneumonie, bei 6 auf 10—15 mg %, bei 4 auf 15—20 mg % und bei 5 auf fast 30 mg %. Die Glykogenwerte blieben im grossen ganzen ebenso lange gesteigert, wie das Fieber andauerte. Bei sonstigen Infektionskrankheiten wurden nur in einem Endokarditis-Fall, in dem der Glykogengehalt 10 mg % betrug, erhöhte Werte festgestellt, dagegen waren die Werte normal bei schwerer Sepsis, bei 6 Fällen von Gelenkrheumatismus, 8 von Pleuritis und 5 von Angina tonsillaris. Desgleichen war der Glykogengehalt normal bei chronischen Infektionen, wie Tuberkulose und Lues.

Wie bereits im Zusammenhang mit der Bestimmungsmethode angeführt, lässt sich von den gesteigerten Werten nicht mit Sicherheit aussagen, ob sie wirklich auf erhöhtem Glykogengehalt beruhen. In Anbetracht dessen, dass sie vorwiegend im Zusammenhang mit Infektionskrankheiten und namentlich Pneumokokkeninfektionen auftraten, ist der Gedanke naheliegend, dass die Ursache wirklich wohl nicht im Steigen des Glykogengehalts, sondern in den Bakterien- und vornehmlich in den Pneumokokkenpolysacchariden liegt.

### Zusammenfassung.

Als Zusammenfassung des Obigen kann festgestellt werden, dass der Glykogengehalt im Blut der Gesunden sehr niedrig ist und auf nur ein paar mg % steigt. Nach Zuckerbelastung und Insulininjektion können in den Glykogenwerten des Blutes keine Veränderungen festgestellt werden, ebenso wenig in nennenswertem Masse im Zusammenhang mit dem Diabetes, so dass dem *Glykogen des Blutes offenbar keine Bedeutung im Kohlehydratstoffwechsel zukommt*. Gesteigerte Glykogenwerte wurden in Material eigentlich nur bei Pneumonie besonders bei kroupöser, festgestellt. Der Verfasser ist jedoch der Ansicht, dass dieser Anstieg mit grosser Wahrscheinlichkeit nicht auf der Erhöhung des Glykogengehaltes, sondern möglicherweise auf den Bakterienpolysacchariden beruht.

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## Über den Wert des Serumbilirubins, bei welchem Ikterus direkt sichtbar wird.

Von

TORBEN K. WITH.<sup>1</sup>

(Bei der Redaktion am 27 April 1943 eingegangen).

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Untersuchungen über den Ikterus-Grenzwert des Serumbilirubins sind bisher nur mit veralteten und ungenauen Analysemethoden durchgeführt worden. Wir haben deshalb dieser Grenzwert mit moderner Methodik (Jendrassik und Gróf's Methode oder With's Mikromethode) untersucht. Unsere Ergebnisse sind in einem Diagramm dargestellt. Das klinische Urteil über das Vorhandensein oder nicht von Ikterus (im Diagramm mit +, (+) und 0 bezeichnet) ist bei den Erwachsenen stets vom Verfasser selbst, bei den Neugeborenen von Dr. E. Hj. Larsen vorgenommen. Es wurden 35 Erwachsene und 46 Neugeborene untersucht.

Das Diagramm zeigt, dass die *Ikterusgrenze für Erwachsene etwa 2.5 mg pro 100 ml ist, für Neugeborene aber bedeutend höher, etwa 9 mg pro 100 ml.*

Dieses eigentümliche Verhältniss ist, soweit uns bekannt, nicht früher beobachtet worden.

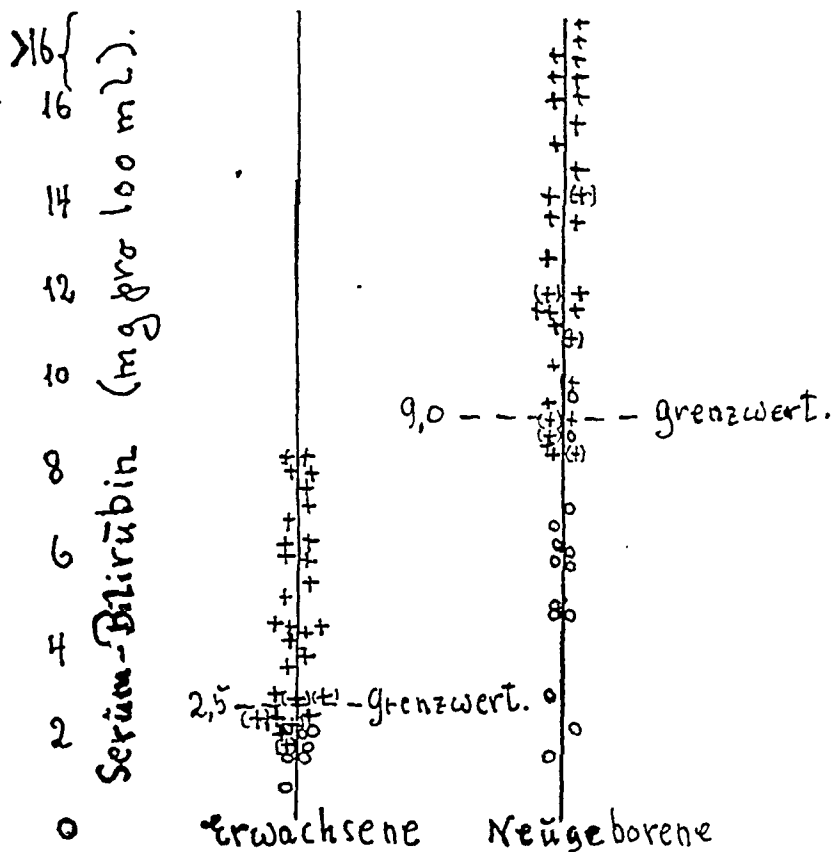
Frühere Untersuchungen über diesen Grenzwert sind spärlich. v. d. Bergh (1918) gibt einen Grenzwert von etwa 2 mg pro 100 ml an. Meulengracht (1920) fand den Grenzwert 10—15 als Ikterusindex gemessen, was

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<sup>1</sup> Die Untersuchungen sind mit Unterstützung von P. Carl Petersens Fond durchgeführt.

ach With (1942, Tabelle 3 und 4) Serumbilirubinwerte zwischen 1 und 2 entsprechen dürfe. Amerikanische Untersucher [Davidson und Mitarb. (1941) Waugh und Mitarb. (1940)] fanden für Neugeborene Grenzwerte von etwa 5 mg pro 100 ml.; sie arbeiteten aber mit Analysemethoden, die zu niedrige Werte geben, und man muss also damit rechnen, dass der wirkliche Grenzwert für Neugeborene noch höher liegt (vgl. Larsen und With).

### Diagramm.



Aus den spärlichen vorliegenden Untersuchungen dürfte man also doch bereits den Schluss gemacht haben, dass der Grenzwert bei Neugeborenen weit höher liegen muss als bei Erwachsenen; man hat aber diese Schlussfolgerung nicht gemacht — wohl weil frühere Untersucher immer entweder Neugeborene oder Erwachsene und niemals diese beiden Patientenkategorien zusammen untersucht haben.

Wir haben die möglichen Ursachen des Unterschiedes der Grenzwerte untersucht ohne zu einer endgültigen Erklärung zu kommen. Erstens könnte man sich denken, dass die Beurteilung des

Ikterus' bei Erwachsenen hauptsächlich an den Sclerae vorgenommen wurde, die Beurteilung bei Neugeborenen dagegen an der Haut; dies muss natürlich sein, da die meisten Neugeborenen ihre Augen fast geschlossen halten. Hierdurch kann ganz gewiss ein gewisser Teil des Unterschiedes erklärt werden, aber nur ein kleiner Teil, da wir viele Erwachsene mit deutlichem Hautikterus und Serumbilirubin zwischen 3 und 4 mg pro 100 ml beobachtet haben. Weiter konnte man denken, dass bei der roten Farbe der Haut vieler Neugeborenen die gelbe Farbe schwieriger zu beobachten sei; da die rote Farbe aber nicht konstant ist und oft nur die ersten Tage nach der Geburt gefunden wird, kann sie kaum eine grössere Rolle spielen.

Eine andere Möglichkeit ist, dass das Bilirubin der Neugeborenen nicht mit dem der Erwachsenen ganz identisch wäre, und zwar in solcher Weise, dass es verhältnissmässig schwächere Gelbfärbung und stärkere Diazoreaktion gäbe. Dadurch konnte eine schwache Gelbfärbung der Haut bei hohen Serumwerten erklärt werden, da die Serumwerte ja bei der Diazoreaktion bestimmt werden. Dass dies nicht der Fall sein kann, geht aber aus den Untersuchungen With's (1942, Tabelle 3) hervor, indem er dasselbe Verhältniss zwischen Ikterusindex und Diazoreaktion (nach Jendrassik und Gróf gemessen) für ikterische Sera von Erwachsenen und Neugeborenen fand.

Noch ein anderer Umstand von einiger Bedeutung ist weiter der hohe Volumenindex des Blutes der Neugeborenen. Nach Vahlquist (1941, S. 180 und S. 183) ist der Mittelwert des Hämatokritwertes des Blutes in den ersten 14 Lebenstagen zwischen 51 und 58, während derselbe für Erwachsene nur etwa 36.7 ist. Das Volumen des Plasmas ist also bei den Neugeborenen nur etwa 40—50 % des Gesamtblutes gegen etwa 65 % bei Erwachsenen. Da infolge Bennholds (1932, S. 339) Untersuchungen — später von Waldenström und Pedersen und auch von den Untersuchungen von Snapper und Bendien bestätigt — die ikterische Farbe der Haut ganz überwiegend durch ihren Blutgehalt und nicht durch Adsorption des Bilirubins an Gewebsteile bestimmt ist, muss man annehmen, dass Neugeborenen (mit 40—50 % Plasma) eine etwa 1.3—1.6 mal ( $65/50 = 1.3$ ) höhere Ikterusgrenze als Erwachsene (mit etwa 65 % Plasma, haben müssen.

Sämtliche oben angeführten Umstände können jedoch kaum die 3 bis 4 mal höhere Ikterusgrenze der Neugeborenen erklären. Auch andere Faktoren müssen Bedeutung haben; z. B. konnte man denken, dass, da alle Neugeborene grössere Serumbilirubinwerte als Erwachsene haben, der klinische Beobachter ganz unwillkürlich eine gewisse Gelbfärbung für normal rechnet und eine stär-

kere Gelbfärbung verlangt als bei Erwachsenen, um über Ikterus zu sprechen. Weiter kann man nicht ausschliessen, dass die Haut der Neugeborenen vielleicht weniger offene Kapillaren und kleine Gefässe als die Haut der Erwachsenen hat, was schwächere Gelbfärbung bei demselben Serumbilirubin mit sich führen sollte.

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## The Importance of Sternal Bone-Marrow Biopsy for the Diagnosis of Familial Acholuric Jaundice.\*

By

A. SØEBORG OHLSEN, M. D., and EJNAR ROELSEN, M. D.

(Submitted for publication March 11, 1943).

The picture of fully developed familial hemolytic icterus with the cardinal symptoms anemia, acholuric jaundice, and splenic enlargement in an individual of a family in which similar cases occur, is so characteristic that the diagnosis nowadays may be said to cause no difficulty. Since the turn of the century, when Minkowski drew attention to this syndrome, the literature about this subject has become so comprehensive that it is difficult to survey it. A good survey of the historical development, clinic, pathophysiology and pathogenesis of the syndrome is supplied for example in the monographs by Meulengracht (1918—22), Gänsslen and co-workers (1925) and Grippwall (1938).

In no small number of cases lacking one or, sometimes, several of the chief symptoms, it may be difficult to make a diagnosis. This also holds for those cases where the chief hematological criterion, the increased fragility of the red-cells in hypotonic saline solutions, is absent.

The osmotic resistance of the red-cells to hypotonic salt solutions is almost always lowered. This reduction may be slight, and several cases even with normal resistance have been observed. Gänsslen reports that 10 of the 100 cases observed by him presented

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\* Paper read in abridged form at the meeting of Dansk Selskab for intern Medicin, May 31st, 1942.



normal resistance. Dawson in accordance with this reports 5 out of 40 cases without decrease of resistance. Meulengracht (1918) likewise emphasizes that this symptom is not pathognomonic. It is possible that these relatively few cases with perhaps only apparently normal osmotic resistance may be disclosed with the help of a quantitative technique such as that suggested by Whitby & Hynes and Creed. Whereas the usual method for determining the osmotic resistance is known merely to establish the incipient and total hemolysis in a number of NaCl solutions of various strength, the mentioned quantitative methods aim at determining the percentage of hemolysis in the single salt solutions. This technique appears somewhat troublesome in the daily clinical work.

What prompted us to commence the examinations of sternal marrow which will be described in the following, was considerations about the amount of importance to be attributed to a moderate decrease of osmotic resistance in a patient who presented anemia, acholuric jaundice, and splenic enlargement.

Before entering into details we shall briefly review the previous investigations in this question.

### Previous Investigations.

It has long been known that familial acholuric jaundice is associated with greatly increased erythropoiesis. The constant hyperhemolysis acts as an indirect stimulus upon the red bone marrow. The clinical condition depends on the greater or less equilibrium between the severity of the destruction processes in the blood stream, particularly the spleen, and the degree of the erythropoiesis. Even though the function of the bone marrow thus actually is just as important a factor in the hemolytic syndrome as the hemolytic processes occurring in the peripheral blood and their reflection, the marrow as an object of examination has not previously been the subject of so much attention as the easily accessible peripheral blood.

When Meulengracht wrote his monograph 24 years ago, there was only one case on record in the literature, namely, Guizetti's case where the marrow was examined. There was found a very hyperactive erythroblastic marrow. At that time Meulengracht wrote: „ . . although there exists only a single examination, it certainly is

warrantable to assume that it illustrates a rule, and that the said finding is typical of the disease...» Subsequently several investigations in bone marrow have been published. Vaughan (1936) in her book mentioned 6 cases, all of which were examined postmortally however.

Since the introduction of puncture of the sternum into the clinic in the nineteen-twenties (Seyfarth), and particularly after the appearance of Arinkin's method of aspiration of the sternal bone-marrow, there have in recent years been published a good many papers about the aspect of the marrow in chronic familial acholuric jaundice. The first case of intravital examination of the marrow was reported by Weiner & Kaznelson (1926). In the marrow blood of that patient were found 63.8 per cent of normoblasts and 11 per cent of nuclei, probably normoblast nuclei. Converted per 400 cells of the «white system», this finding corresponds to 705, or rather 1187, normoblasts. Similar results were reported by Dameshek (3) (2 cases), Löwinger (6 cases), and de Weerd (6 cases). The greatest number of erythroblasts was reported by Tötterman who in his patient found 1893 nucleated «red-cells» altogether per 400 «white».

The results of these investigations are perfectly alike. All show an exceedingly increased erythropoiesis, but without signs of lacking maturation of the erythrocyte prophaes. Only Tötterman has in his patient observed a single megaloblast. Both Löwinger and de Weerd report lacking parallelism between the degrees of anemia and erythropoiesis.

### The Authors' Examinations.

The patient with whom our investigations commenced, presented the typical symptoms of chronic acholuric jaundice, but only a very moderate or doubtful decrease of the osmotic resistance of the erythrocytes.

The patient was a 10 year old girl: K. A. S. G. Medical Department B. Case report No 1436/41, 15/8—13/11 41, and 15/9—30/9 42. Only child of healthy parents. No similar cases in the family. History of antecedent varicella and whooping cough. Since the age of 4, recidivating bronchitis.

It is reported that the child has had icterus «for a long time», at any rate 18 months. During that time there are reported frequent attacks of pains of uncharacteristic nature in the abdomen. Scarcely any rise of temperature. Stools not acholic. Urine not dark in colour.

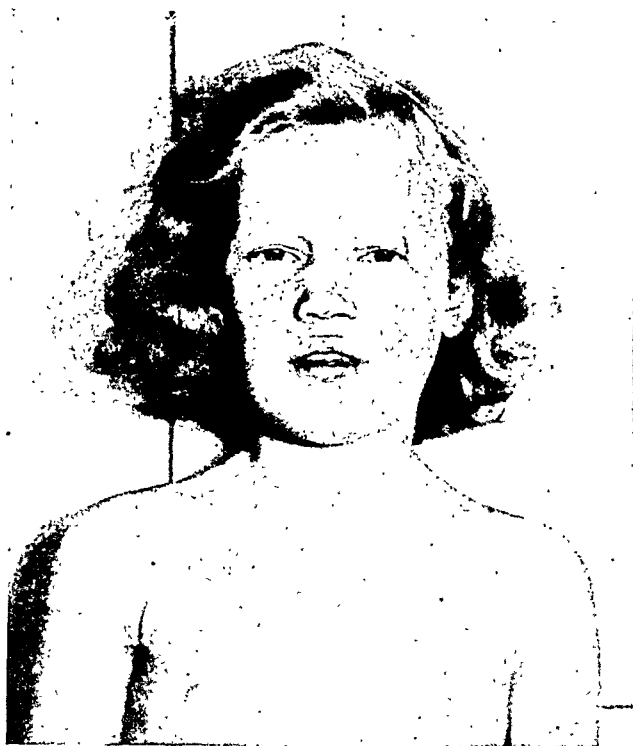


Fig. 1.

*Objective examination:* Very pale, fair, overgrown girl of somewhat «asiatic» appearance (see Fig. 1).

Nutrition fairly good. There is distinct scleral icterus, doubtful icteric colour of the skin. Skull, eyes, ears, nose, nothing abnormal. Throat normal. Tongue slightly furred, moist. Teeth good, but the upper incisor teeth with concave, slightly irregular borders (after a dental fracture incurred a twelvemonth ago). At the anguli, lymph nodes the size of a hazelnut. Otherwise no demonstrable glandular swelling. Stethoscopy of lungs and heart normal. Abdomen a little big, the lower segment bulging out somewhat. Liver not enlarged, the apex of the spleen, however, being palpable just below the left costal margin, particularly on deep inspiration. No ascites. Spine normal. Off pars lumbalis, a well developed knot of hair. Extremities normal. Patellar reactions normal. The skin somewhat dry everywhere.

*Special examinations:* Height 140 cm. Weight 30 → 34.5 kg. Temperature normal. Urine of normal colour, without albumin and sugar; + urobilin 1: 10, varying up to 1: 100. On admission: Hb. 51 %. Red blood corpuscles 2.17. Colour index 1.11. Volume index 1.03. Microscopy of erythrocytes: Mean 7.6  $\mu$  (max. 9.5, min. 4.4). Halometry: 7.6  $\mu$ . *White blood corpuscles:* 2000. Smears: Polymorphonuclear 53 per cent, eosinophils 3 per cent, lymphocytes (large) 4 per cent, lymphocytes (small) 36

Table 1.

Date	Incipient hemolysis	Total hemolysis
21/8 41	at 0.52 per cent	at 0.40 per cent
22/8 »	» 0.52 » »	» 0.38 » »
5/9 »	» 0.48 » »	» 0.28 » »
18/9 »	» 0.48 » »	» 0.24 » »
10/10 »	» 0.46 » »	» 0.34 » »
24/10 »	» 0.48 » »	» 0.34 » »
15/1 42	» 0.52 » »	» 0.38 » »
9/4 »	» 0.48 » »	» 0.32 » »
26/5 »	» 0.54 » »	» 0.30 » »
4/9 »	» 0.50 » »	» 0.40 » »
7/10 »	» 0.48 » »	» 0.30 » »

per cent, monocytes 3 per cent, plasma cells 1 per cent. Moderate anisopoikilocytosis. ++ polychromasia. Reticulocytes about 50 to 95 per mille. Thrombocytes 205,000. Icterus index (Meulengracht) 30. Bilirubin determination *a. m. van den Bergh*: + indirect, no direct reaction.

Several blood examinations performed during the hospital stay substantiated the above-recorded values: S. R. 13—5 mm. *Wassermann* reaction and *Kahn* reaction negative. *Mantoux* (1/10 mgm.) negative. Galactose test (performed twice) (administered 40 g): (1) excretion of 1.63 g), (2) no excretion of galactose.

The osmotic resistance of the erythrocytes is evident from Table 1.

x-ray examination of lumbar spine: Spina bifida of lumbar vertebra V. x-ray of skull and long tubular bones (May 1942, when the clinical condition was exactly the same as on admission) disclosed no pathological bone processes such as may be found in various forms of hemolytic anemia, especially Cooley's erythroblast anemia.

Examination of the parents:

Mother: Hb. 115 per cent. Icterus index 2. Osmotic resistance: 0.52. → 0.36.

Father: Hb. 112 per cent. Icterus index 5. Osmotic resistance: 0.52 → 0.36.

**Summary:** In a girl, aged 10, of healthy parents, are found (1) severe anemia, (2) icterus, (3) splenic enlargement, (4) reticulocytosis, (5) positive indirect and negative direkt van den Bergh reaction, (6) acholuria and positive urobilin reaction, (7) doubtful or slight decrease of the osmotic resistance of the erythrocytes, and (8) normal micrometry.

Table 2.

*Sternal punctate from patient No. 1.*

400 cells of the white system were counted. The numbers represent the per-  
centual distribution, the bracketed numbers representing mitoses.

Date	9/9 1941	21/10 1941
Myeloblasts .....	1.75	0.50
Promyelocytes .....	2.50	0.75
Neutrophilic myelocytes .....	31.75	23.25
Eosinophilic myelocytes .....	7.25	5.00
Basophilic myelocytes .....	0	0
Metamyelocytes + leukocytes with rod-shaped nuclei .....	19.75	36.00
Polymorphonuclear neutrophilic leukocytes ....	10.25	18.50
Eosinophilic leukocytes .....	2.00	0
Basophilic leukocytes .....	0	0
Lymphocytes .....	22.50	15.50
Monocytes .....	0.25	0
Plasma cells .....	0.25	0
Megakaryocytes .....	0.75	0.50
Reticular cells .....	0.00	0
On 400 cells of the «white system»:		
Erythrogonia .....	88 (1)	96 (6)
Erythroblasts (basophilic) .....	463 (5)	371 (8)
Erythroblasts (eosinophilic) .....	875	868
Megalogonia .....	0	8

*Diagnosis:* On the ground of the clinical picture and the result of the examinations, we thought there was a question of a so-called isolated case of chronic hemolytic icterus with but slight decrease of resistance. Other forms of hemolytic anemia we did not think it necessary to take account of. From a hematological viewpoint, there might be reason to take Lederer's anemia into consideration but, on account of the distinctly chronic course of our patient's disease, we thought it warrantable to pay no regard to that either. Infantile or congenital liver cirrhosis is mentioned merely for theoretical reasons. The picture is not consistent with it at all, amongst other things because of the absolutely negative result of the galactose test. In order, however, to insure our diagnosis, we submitted our patient to sternal puncture. The results of the puncture and of a reexamination are recorded in Table 2.

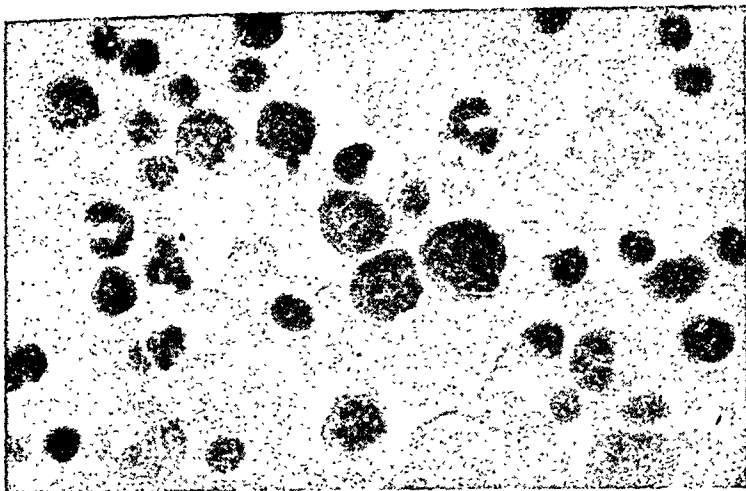


Fig. 2. *Sternal punctate from patient No. 1.*

Microphoto, enlargement 1: 800.

Note the numerous erythroblasts and several erythrogonia.

In both punctates the red corpuscles were strongly coloured and presented pronounced anisocytosis and polychromasia. The first punctate presented some macrocytosis. Fig. 2, a microphoto of the marrow blood (9|9), will serve to illustrate Table 2.

This picture of exceedingly hyperactive bone marrow substantiates our diagnosis: Chronic acholuric jaundice. It agrees with the descriptions of marrow which have been published in connection with this syndrome.

*Course:* The parents strongly objecting to surgical treatment, we temporized at first. During her entire hospital stay, the patient received ferrum reductum 0.5 g. 3 times daily but without any essential effect on the Hb. per cent. In the interim between the two hospital stays, she received, besides the same dose of iron, intramuscular injections of «extr. hepatitis Gea» 2 cm<sup>3</sup> (corresponding to 100 gr. liver) every 2nd to 3rd week, likewise without any effect on the condition. After her discharge, she reported repeatedly for control as out-patient. Hb. per cent slightly fluctuating, as a rule amounting to about 65. In the summer of 1942 (after an attack of measles) she was more exhausted. The condition in September (a twelve-month after the diagnosis had been made) being unchanged and the patient both physically and psychically being at a stand, the parents gave permission for operation. On 3/10, in the surgical department A, splenectomy was performed (H. Bjerre, M. D.); the spleen weighed about 300 gr. On 7/10, another sternal puncture was performed. The result is recorded in Table 5 and will be discussed later. Icterus index 4 days after the operation: 5. Reexamination about 2 months after the operation: Relative

Osmotic resistance patient total		Blood platelets per mm <sup>3</sup> of plasma	Leuko- cytes	Uro- bilin- uria	Splenic enlarge- ment	Remarks
1.60	0.40	272,000	6,120	+	—	Mother «always yellow». Operation for gall-stones 24 years ago. Always recidivating anemia and icterus. Manages her hospital work satisfactorily but she «never feels perfectly well as others».
0.72	0.50	280,000	5,000	—	+	Sister of pat. No. 2. Likewise operated for gall-stones 23 years ago. Her condition throughout the years the same as that of No. 2, her working-power, however, somewhat decreased. Recently, she has suffered from slight hypertension.
0.60	0.40	260,000	4,620	+	+	Admitted to hospital on account of periodical pains under the left costal margin. Missed a good many days of school attendance. «Always yellowish». The paternal grandfather, father and a sister suffer from the same disease. Clinical condition at present satisfactory.
0.68	0.48	243,000	5,120	+	+	Father of pat. No. 4. Always reacted strongly to infectious diseases. On performing hard work, especially brain-work, he readily becomes tired and yellowish. His clinical condition at present satisfactory.
0.54 (0.56)	0.40 (0.38)	190,000	6,200	+	+	At the age of 3—4 short of breath and tired by playing. Examination by specialist who detected «heart-complaint». During the last 9 months sluggish and listless. No known cases of acholuric jaundice in the family. Nothing surely abnormal at the heart except great systolic extension in the middle of the precardium and over the pulmonal artery. x-ray of heart: Nothing abnormal. EKG nothing reliably abnormal. After splenectomy: Wellbeing.
0.72 (0.70)	0.50 (0.48)	—	— (8,800)	+	+	During the last 4 years, recidivating icterus. After splenectomy, no such symptoms.
0.66 (0.62)	0.44 (0.36)	450,000 (572,000)	10,360 (6,000)	— (—)	+	Sister of pat. No. 4. Always yellow. The intensity of the jaundice has fluctuated, periodically exacerbating with pronounced tiredness. Feels well since splenectomy was performed a twelvemonth ago. Still, she suffers from periodical tiredness.

Table 4.

*Examination of sternal bone-marrow from 6 patients with chronic acholuric jaundice.*

400 cells of the «white system» were counted. The numbers represent the per-centual distribution, the bracketed numbers representing the number of mitoses.

Patient No.	2	3	4	5	6	7
Myeloblasts .....	2.5	0.25	0.5	1.0	3.25	4.5
Promyelocytes .....	1.5	2.0	2.0	1.25	0.5	2.25
Neutrophilic myelocytes	23.5	28.25	20.0 (2)	19.0	23.25 (2)	20.25
Eosinophilic myelocytes	2.0	0.25	4.5	1.75	2.25	2.75
Basophilic myelocytes ..	0	0	0	0	0	0
Metamyelocytes + leuko- cytes with rod-shaped nuclei .....	24.5	30.5	26.75	33.25	24.5	28.25
Polymorphonuclear neu- trophilic leukocytes ..	32.25	21.75	24.75	25.5	13.5	26.00
Eosinophilic leukocytes	0.25	1.25	0.75	1.25	1.25	0
Basophilic leukocytes ....	0	0	0	0	0	0
Lymphocytes .....	13.50	15.75	20.5	16.25	31.5	3.75
Monocytes .....	0	0	0	0.5	0	0.25
Plasma cells.....	0	0	0	0	0	0
Megakaryocytes .....	0	0	0	0.25	0	0
Reticular cells .....	0	0	0.25	0	0	0
On 400 cells of the «white system»:						
Erythrogonia .....	10	29	14	21 (1)	25	24
Erythroblasts (basophilic)	129 (6)	171 (7)	76 (1)	144 (7)	209 (4)	162 (8)
Erythroblasts (eosino- philic) .....	315	308	138	261	90	214
Megalogonia .....	4 (1)	a few	0	1	0	6

from the others by presenting, just as pat. No. 1, only a moderate decrease of resistance. It is also interesting that pat. No. 6 presented the same somewhat peculiar «asiatic» phenotype as our patient No. 1 (see Fig. 3),

The results of the sternal bone-marrow biopsy are recorded in Table 4.

To draw a parallel with the conditions of the marrow in normal individuals, the results are recorded graphically in a diagram (Fig. 4) including as normal values the mean values from T. Svend Hansen's work about the bone marrow in the normal.



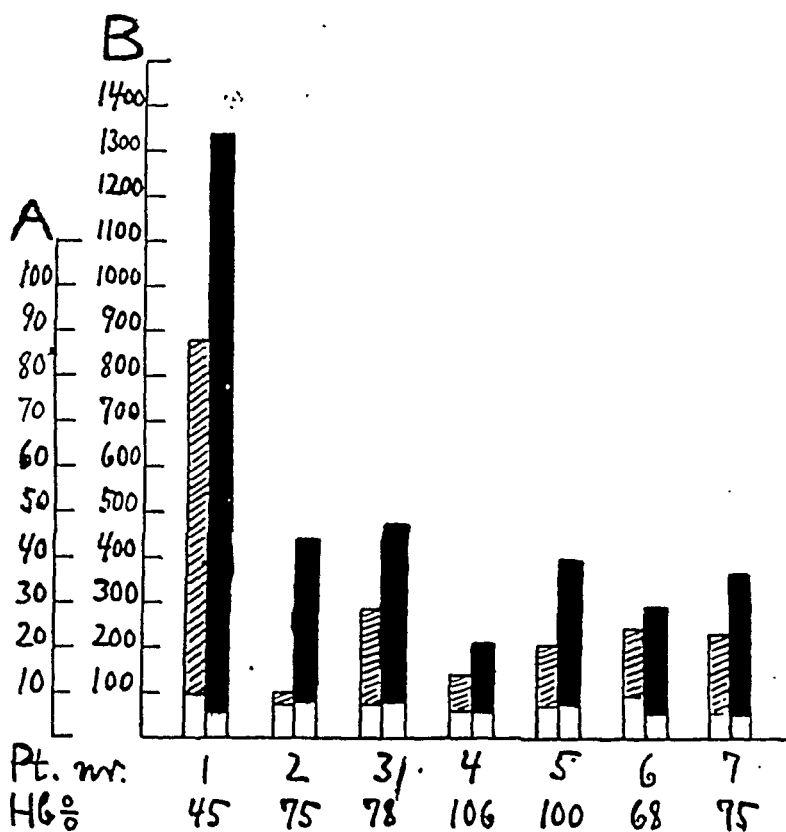


Fig. 4.

A: Number of erythrogonia. B: Number of erythroblasts. Hatched column = erythrogonia. Black column = erythroblasts. White column = normal values.

From this survey, and especially from the diagram, it will be seen that the erythropoiesis in all the patients was very considerably increased, even though not so extraordinarily as in pat. No. 1. Whereas the erythroblast concentration in the marrow blood of our first patient showed an increase of nearly 2500 per cent, our other patients presented a far more moderate, yet very pronounced increase of the erythroblast concentration amounting to from 250 to 600 percent. With one exception (pat. No. 2) the erythrogonium concentration was likewise greatly increased, though not nearly so much as in patient No. 1. It might appear as if there were a certain correlation between the severity of the anemia and the degree of the erythropoiesis. We are not convinced of it however. Nor is it corroborated by other investigators. We shall revert to it later.

Just as other authors, we must admit that a difference between the erythroblasts in acholuric jaundice patients and the erythro-

Table 5.

*Examination of sternal bone-marrow of 4 splenectomized patients with acholuric jaundice (the cell numbers being the numbers of «red-cells» counted per 400 counted cells of the «white system»).*

Patient No.	1	6	7	8
Hb. per cent .....	91	110	90	128
Time elapsed after splenectomy ..	3 days	10 days	3 weeks	about 1 year
Erythrogonia .....	9	16	8	12
Erythroblasts (basophilic) .....	125 (5)	13 (1)	70 (3)	67 (5)
Erythroblasts (eosinophilic) ....	70	25	81	102

blasts of the normal is not detectable. We must emphasize that, when the anisocytosis is considerable, the marrow is found to contain not only small but also large erythroblasts, which may conveniently be named macroblasts. By the differential count of the various marrow preparations, the red blood corpuscles are often found to be small, stained fairly intensely in the center, corresponding to the microspherocytosis. Moreover, anisocytosis varying according to the degree of the erythropoiesis, and often pronounced polychromasia are seen.

It is very interesting that a few true megalogonia were found in the marrow blood of several patients (Nos. 1, 2, 3, 5, and 7). This phenomenon will later be discussed in detail.

With regard to the «white cell system» it shall be mentioned that slightly increased leukopoiesis is frequently observed in these patients, quite normal findings not being infrequent however.

To (2). In Table 5 are recorded the results derived from examinations of marrow from patients with acholuric jaundice after splenectomy. Our material comprises 4 patients, and the numbers refer to those in Table 3.

On comparing Table 5 with Tables 2 and 4, the striking change in the bone marrow of the 4 splenectomized patients immediately becomes evident. The bone marrow which had been distinctly hyperplastic has become but slightly so, almost like normal marrow. The diagram, Fig. 5, compared with Fig. 4 will illustrate this.

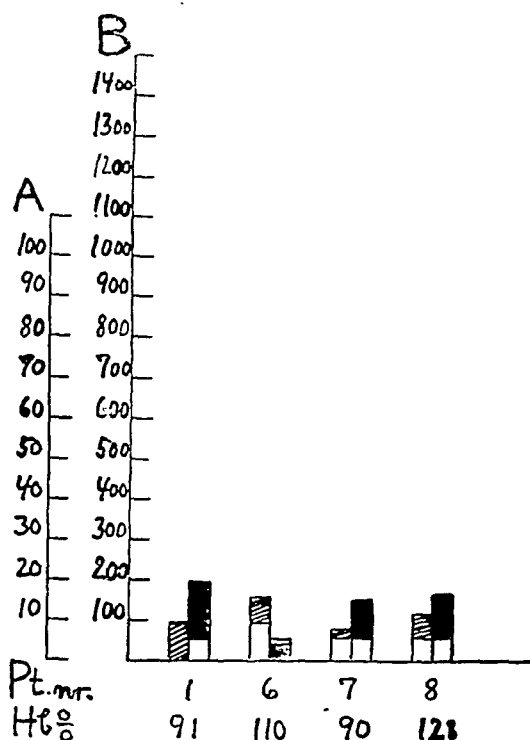


Fig. 5.

A: Number of erythrogonia. B: Number of erythroblasts. Hatched column = erythrogonia. Black column = erythroblasts. White column = normal values.

To (3). To make sure that the increase of the erythropoiesis was not due to the jaundice, we examined 2 patients with acute hepatitis and a degree of icterus corresponding to that of our patients. In both of them were found normal bone marrow conditions. Only the picture of the red bone marrow will be recorded (Table 6).

Table 6.

Number of cells found per 400 cells of the «white system».

Case report No.	1413/41	1451/41
Erythrogonia .....	13	1
Erythroblasts (basophilic).....	19 (1)	15 (1)
Erythroblasts (eosinophilic).....	52	40

## Discussion.

Just as other authors, we find, by sternal bone-marrow biopsy, in patients suffering from chronic acholuric jaundice that the erythropoiesis is increased extraordinarily. In all our patients whose clinical condition with one exception was relatively satisfactory when the examination was performed, we found that the erythropoiesis had increased by several hundred per cent as compared with the normal. Only in a single patient (No. 1) did we find an exceptionally increased erythropoiesis, the erythroblast concentration in the marrow blood, similarly to Tötterman's case, presenting an increase of about 2500 per cent. A common feature of these two cases is that they probably represent acquired or isolated chronic acholuric jaundice.

As was mentioned before, these great individual differences in the erythropoiesis do not run parallel with the individual differences in the severity of the anemia. The individual differences in the strength of the erythropoiesis must be sought in individual differences in the severity of the hemolytic processes and the degree of inhibition of the marrow. The anemia on the other hand depends on all these three components. The balance between these three factors is decisive of the clinical condition. It is obvious that a bad clinical condition of long standing (as in pat. No. 1) associated with a low Hb. percentage, paralleled with constant extraordinarily increased erythropoiesis, must be the expression of an abnormally strong hemolysis of the erythrocytes in the blood stream or of an enormous inhibition of the marrow, or a combination of both.

In this connection it shall be mentioned that the very degree of decrease of the osmotic resistance scarcely is a measure for the hemolytic processes. As was mentioned, the osmotic resistance in patient No. 1 was but slightly or doubtfully decreased. The result of the examination of the marrow, the enormous erythropoiesis, may well be interpreted as the expression of a strong reaction to severe hyperhemolysis. Considering, on the other hand, that the number of leukocytes in our pat. No. 1 constantly was low, on isolated examinations below 3000, mostly between 3000 and 4000, the marrow picture also must probably in some degree be the result of a splenogenous marrow inhibition. Lack of iron as cause of a possible inhibition of normal maturation of the erythrocytes, as

that observed in simple achylic anemia, is out of the question. Iron therapy, as was mentioned, had no effect on the anemia.

A fact which deserves attention is that we in several cases found megalocgonia, corresponding to Tötterman's megaloblasts. In general it may be said that the erythropoiesis in chronic acholuric jaundice is distinctly erythroblastic, thus being diametrically opposed to the marrow in pernicious anemia. This latter, as is wellknown, is characterized by a pronounced megaloblastic type of regeneration. In Vaughan's book, Turnbull thoroughly describes the appearance of the marrow in chronic acholuric jaundice. In 3 out of 6 cases of chronic acholuric jaundice submitted to necropsy, microscopy of the marrow disclosed megaloblasts. In two of these cases there was a question of »considerable» quantities of these cells. Both these patients had died in sequel to a crisis. Turnbull declares that this shows that the erythropoiesis in chronic acholuric jaundice *may* become megaloblastic, and thus resemble the erythropoiesis in pernicious anemia. The megaloblastosis observed need not be due to a hemolytic crisis. It *may* be the cause of a hemolytic crisis. According to Turnbull, it may be assumed that the hemolysis in chronic acholuric jaundice is compensated by a greatly increased normoblastic erythropoiesis, provided that the necessary A. P. factor is present. If this factor somehow or other is absent, megaloblastic erythropoiesis will appear. Thus the appearance of cells of the megaloblastic regeneration type probably is a warning, exhorting to active intervention (splenectomy), at any rate to closer observation of the patient.

The question now arises whether the marrow, in chronic acholuric jaundice, has undergone such characteristic changes that definite diagnostical conclusions can be derived from sternal bone-marrow biopsy in patients who are observed for this syndrome. In our opinion, this question may be answered in the affirmative. In this connection it will be practical to recapitulate those forms of anemia which are attended with *strong* erythroblastic regeneration in the bone marrow. Slightly increased erythropoiesis is met with in most forms of anemia. Above all it is wellknown that the erythropoiesis is distinctly increased in simple achylic anemia. Several authors (13, 2, 20, 24, 22) have examined this question with the help of sternal bone-marrow biopsy. According to those authors, the marrow blood of persons with this syndrome contains from

about 25 to 50 per cent of erythroblasts. The erythrogonium number is reported to be normal however. An increase of the erythroblast concentration to 50 per cent of the total number of cells is of the same magnitude as in some of our patients with acholuric jaundice. Such numbers are exceptions. Thus in Segerdahl's 10 patients 28.6 per cent was found on an average. Also in other forms of anemia, the erythropoiesis may reach heights similar to those found in achylic anemia. Segerdahl thus particularly reports hemorrhagic anemia just as Reimann who likewise stresses the increased erythropoiesis in »agastic» anemia (after resection of the stomach) and anemias after different forms of enteritis. Buus Hansen recently published 3 cases of anemia after ingestion of litharge, with pronounced erythroblastic changes of the bone marrow. Here, too, the erythroblast values are on the same level as those which we find in acholuric jaundice, whereas the number of erythrogonia, just as in the other anemias mentioned, is but slightly increased or within the normal limits.

There are thus several anemic conditions, in which the bone marrow presents considerable erythroblastic hyperactivity. The highest degrees of erythropoiesis, however, are no doubt met with in chronic acholuric jaundice. This is evidenced by the fact that this syndrome regularly is associated with an increase of both erythroblasts and erythrogonia.

Even though these similarities of the marrow pictures found in different forms of anemia, in *certain* cases *perhaps* are great, they do not detract from the value of the examination of the bone marrow as a differential-diagnostic aid in acholuric jaundice. When there is a question of this syndrome, there will be at our disposal certain clinical data and laboratory criteria that will help us to exclude other anemic conditions.

Of considerable interest is our observation of the appearance of the bone marrow after splenectomy. The violent erythropoiesis ceases in the course of a very brief space of time. Instead of it appears a slightly though definitely hyperactive red bone marrow. This is a parallel to the changes of the osmotic resistance and of the form of the red cells before and after splenectomy. From several works (19, 11, 14, 6), it is a wellknown fact that the decrease of the osmotic resistance and the microspherocytosis persist after splenectomy, even though both these functions change towards

the normal. Complete normalization is out of question except in acquired or isolated cases where it was observed by Heilmeyer after splenectomy. The fact that the increase of the erythropoiesis persists after splenectomy indicates, just as the persistent decrease of the osmotic resistance and the persistent microspherocytosis, that in acholuric jaundice there is a question of a hyperhemolytic action not only from the spleen but also from other organs, probably the entire reticulo-endothelial system. This opinion was already expressed in Meulengracht's monograph of 1918. On the other hand, this persistent hyperactivity of the bone marrow might, perhaps, be utilized for the original conception of the pathogenesis of chronic acholuric jaundice, which was advocated particularly by Chauffard and which, as is known, terminated in the chief point of the syndrome being an abnormality in the erythrocytes themselves. As was previously mentioned, however, there is no clue to the pro phases of the erythrocytes in acholuric jaundice differing from those cells which are observed in normal erythropoiesis. The results of our investigation may thus be explained by the hemolysis theory, whereas, on the other hand, they do not positively support the theory of the primarily changed erythrocytes. This discussion of the pathogenesis will not be entered into, however. It shall merely be mentioned that the different authors are far from agreeing about this point. Recent authors seem to side with the hemolysis theory (Lepel, Dameshek & Schwartz, Heilmeyer).

Finally it shall be emphasized that the number of blood platelets was found to be normal in all those of our patients examined. This agrees with the reports of other investigators. We have found but one exception, namely, Löwinger's patient No. 1, whose number of platelets prior to splenectomy amounted to 70,000 and only became normal after it. These platelet findings in patients with so pronounced a blood regeneration do not support the theory according to which the platelets originate from the erythrocytes.

### Summary.

1. In a 10 year old girl who presented a so-called isolated case of chronic acholuric jaundice without definite or with but slight decrease of the osmotic resistance of the erythrocytes, sternal bone-marrow biopsy revealed an extraordinary increase of the erythro-

poiesis. The erythroblast concentration was increased to 2600 per cent of that corresponding to the patient's age, whereas the number of erythregonia had increased by about 800 per cent.

2. Greatly increased erythropoiesis was likewise found in 5 patients with typical chronic acholuric jaundice. The erythropoiesis was not so strongly pronounced as in the first-named patient. The erythroblast concentration was increased by about 250 to 600 per cent, the number of erythregonia with one exception being increased by about 100 to 300 per cent. In a single patient with chronic acholuric jaundice without typical decrease of resistance, the erythropoiesis was found to be of the same magnitude.

3. Sternal bone-marrow biopsies performed after splenectomy (4 cases) disclosed slightly though definitely increased erythropoiesis.

4. The increase of the erythropoiesis observed in chronic acholuric jaundice is far greater than in other anemic conditions, for example in simple achylic anemia and hemorrhagic anemia. In these conditions, the number of erythregonia is not increased, and the erythroblast concentration as a rule is considerably less increased. The picture of the marrow found in chronic acholuric jaundice is so characteristic that sternal bone-marrow biopsy henceforth must play as great a part as a differential-diagnostic aid as the usual laboratory criteria (the decrease of the osmotic resistance, microspherocytosis, reticulocytosis and Hijman van den Bergh's reaction) which are and remain so valuable in this syndrome.

5. In a few patients the marrow was found to contain isolated cells of the megaloblastic regeneration type (megalogonia). This finding is discussed on the ground of Turnbull's investigations. It probably is an exhortation to close control of the clinical state, eventually to active intervention (splenectomy).

6. The persistently increased erythropoiesis found after splenectomy, even though of moderate magnitude, is suggestive of this syndrome being associated with hyperhemolytic processes in other organs than in the spleen, probably in the entire reticulo-endothelial system. This agrees with the persistence of the microspherocytosis and of the decreased osmotic resistance of the erythrocytes after splenectomy.

7. In 7 of our patients the number of blood platelets was found to



be normal. This finding is inconsistent with the conception of the origin of the blood platelets from the erythroblasts.

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## Serum-Iron in Scurvy

and the Influence of Ascorbic Acid on Iron Resorption in  
Chlorosis and Achylic Anemia.

By

Aa. VIDEBÆK and G. ALSTED.

(Submitted for publication April 13, 1943).

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Anemia is a constant symptom of scurvy, but its cause is debatable. Is it due to the factor that is so important to the diagnosis of scurvy: hemorrhage (though this must on the whole be described as very moderate), or is it due to a slight or abolished irritant (the C-vitamin itself) for erythropoiesis? It is possible that anemia is due to necrosis of the marrow with circulatory disturbances as described by Turnbull, or perhaps they are right who hold that anemia in scurvy is simply due to the fact that a diet poor in C-vitamin is also poor in iron (Abt, Liu & Chu et al.). A C-vitamin deficiency is thought to reduce the resistance to infection, for which reason Hansmann believes that anemia is the result of intercurrent infections. On the other hand, Faulkner suggests that the cause of the anemia occurring with many infections is the result of a relative C-vitamin deficiency. Mettier, Minot & Townsend and Parson show in children and adults respectively that scurvy anemia reacts but sluggishly to iron treatment, whereas in patients suffering from scurvy, C-vitamin causes a prompt answer with reticulocytosis and a rapid increase of the haemoglobin percentage in the blood, whereas no similar effect was obtained either with large doses of iron or with large quantities of C-vitamin-free liver extract. With

iron ascorbate in very small doses (50 mg daily) Lorenz obtained a pronounced antianemic effect and therefore considered that C-vitamin exerts a specific effect on erythropoiesis. In this connection it may be added that C-vitamin has no effect on pernicious anemia (Vaughan). Thus, whereas it seems evident that scurvy anemia responds to treatment with ascorbic acid, its exact mode of action is still unclear.

More recent investigations suggest that the apparent specific effect of C-vitamin depends at any rate to some extent on the fact that ascorbic acid facilitates the absorption of iron from the intestine. C-vitamin is strongly reducing and therefore may promote absorption by the conversion of the slowly-absorbable ferri-compounds to readily-absorbable divalent iron. Koch has made determinations on the serum-iron level and by means of C-vitamin perorally obtained an increased absorption of iron, especially in pernicious anemia. Lucksch, however, considers that this effect is an indirect one, for gastric secretion is stimulated. Schröder & Braun-Stappenbeck also indicate that the C-vitamin has an essential part to play in the absorption of iron, for they find extensive parallelity between serum's content of C-vitamin and of iron in a number of different physical conditions. By administering C-vitamin orally they succeeded in raising the serum-iron level, whereas this was not apparent after giving ascorbic acid intravenously.

However, there are no published investigations on the serum-iron level in scurvy. Its position is unquestionably of some interest and justifies the communication of the following:

In the spring of 1942 we had the unusual experience of having four patients admitted to Department B with clinically manifest scurvy. Three of them were elderly old men living alone in straitened circumstances and finding their own food. All four patients presented the classical clinical symptoms of scurvy: hemorrhages, muscular tenderness, and anemia; one had pronounced gingivitis. They thus conformed exactly to the cases described by Meulengracht.

Table 1 contains the values for serum-iron (Heilmeyer & Plötner's method), serum ascorbic acid (Wahren) and the hemoglobin percentage (Sahli) for the four patients, who on hospitalization all had a hemoglobin percentage of lower than 60 and a serum ascorbic acid value of 0 or nearly so. Based upon his own investiga-

Table 1.

	Days after hospit'n.	Serum- iron in $\gamma\%$	Serum ascorbic acid in mg %	Hb %	Col. Index.
C. R. ♂ 70 years 1180/42	1	42	0.06	60	0.85
	8	63	0.15	63	0.93
	18	63	0.41	66	0.92
	25	89	0.70	64	0.89
V. P. ♂ 66 years 968/42	3		0.00	50	1.04
	10		0.03	58	
	14	36	0.38	55	1.07
	17	56	0.64	71	
	28	51	0.61		0.94
L. P. P. ♂ 57 years 1150/42	35		0.87	80	0.99
	5	42	0.03	42	1.03
	12	84		65	0.93
	26		0.12	75	1.04
L. L. ♂ 64 years 1038/42	29	63	0.44	75	
	4	35	0.00	53	0.78
	11	35	0.15	50	0.64
	18	49	0.12	65	0.80
	21	43	0.23	72	0.83

tions and those of others Vahlquist places the lowest limit of the normal value of serum-iron at 50  $\gamma\%$  and it will be seen from the table that lower values were found in all four cases when the patients were admitted here. They were treated with both ascorbic acid and iron, so that the values for serum-iron and hemoglobin percentage rose, though slowly.

In these four cases of scurvy the anemia may have been due to iron deficiency, whether it was the result of a binding of the iron in the reticulo-endothelial system, which one sees in infections, malignant tumours and Hodgkin's disease, of a hemorrhage (increased secretion) or of a reduced iron absorption. Schmorl, Harris, Fraenkel and Vaughan, however, on making a microscopic examination of bone marrow in cases of scurvy found reduced action of the hemopoietic tissue; it is true that this does not preclude the first possibility, but it makes it less probable. The possibility of binding in the reticulo-endothelial system cannot of course be ruled out. In these four cases hemorrhage alone will not explain the low serum-iron values, and the marrow picture in scurvy argues that the

anemia was not due to bleeding. It is possible that these low values are the result of reduced iron absorption from the intestine, either because the iron content of the food was low or because the C-vitamin in some way has an influence on the iron absorption which, if there is a deficit of ascorbic acid in the ingested food, will be inhibited. As pointed out by Vahlquist, however, there are so many hitherto unknown factors in the mechanism that regulates serum-iron that it is difficult to say that the cause of anemia accompanied by low serum-iron is a deficiency in iron.

In the first three of our cases the almost normal colour index seems to argue against anemia caused by iron deficiency, and in all four cases both blood regeneration and increase of serum-iron seem to proceed more slowly under treatment than is usual with this form of anemia. But as all the patients were also treated with ascorbic acid, the conclusions that can be drawn as to the effects of the iron treatment must necessarily be limited.

In order to see if there is any connection between the ascorbic acid in the blood and the iron in serum we shall report on three cases of anemia due to iron deficiency treated first with ascorbic acid alone, orally, then with a ferri-compound, followed by treatment with both ascorbic acid and ferri-salt. In all cases the treatment terminated with ferrous tartrate.

These cases were two young women with chlorosis (essential juvenile iron deficiency anemia) and an older woman with simple achylic anemia. A brief extract of their case reports will be given below together with the results of the more important examinations. Treatment and its results appear from the tables and the diagrams.

**No. 1.** E. K. M. ♀, 28 years, unmarried shop assistant. Had diphtheria when ten years old, and pneumonia when fourteen. Menses from fifteen, always regular. During past year otosclerosis duplex. Hospitalized because for six months she had been tired and dizzy, with faintness and palpitation. Her diet had been somewhat sparse, but varied.

*Physical examination:* Asthenic type, weight 53,5 kg., height 163 cm. Hearing impaired. Teeth somewhat defective. Heart: Systolic murmur all over the precordium, otherwise normal. Wassermannreaction negative. Gonococcus complement fixation test: negative. Blood pressure: 120/60. Benzidine reaction on stools, repeatedly negative. Urine: nothing abnormal. X-ray of stomach: no sign of ulcer, stomach slightly slack. X-ray of lungs: nothing abnormal. Gynaecological examination: natural. Ewald

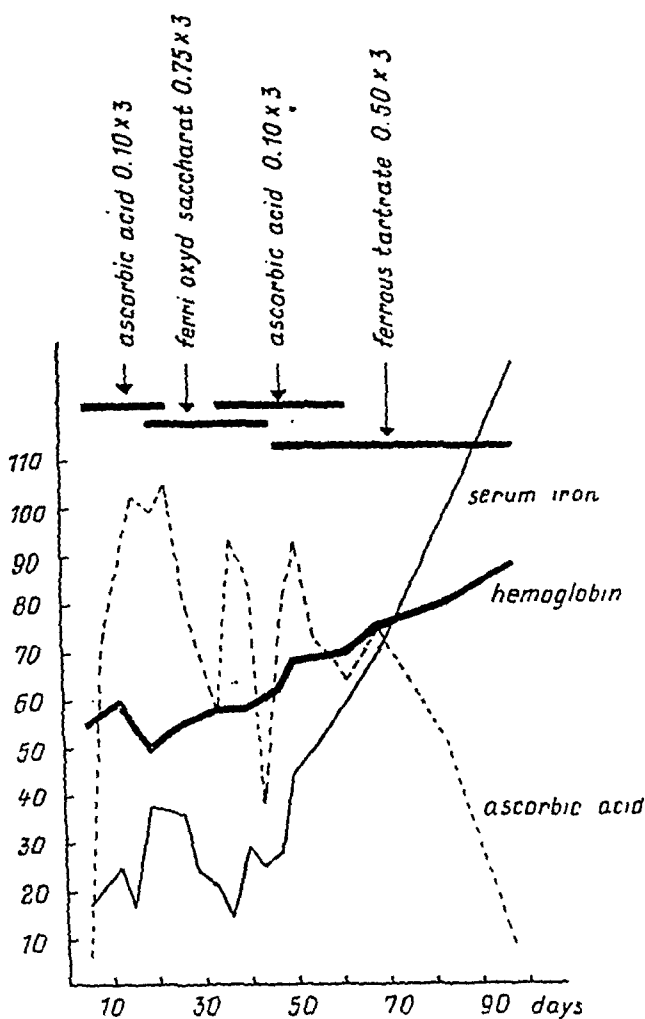


Diagram 1.

The abscissa indicates the time in days; the ordinate indicates hemoglobin in per cent, ascorbic acid in mg per cent and serum iron in  $\gamma$  per cent. (1  $\gamma$  = 0.001 mg).

test meal (20 mins.): 114, free acid: 0. total acidity: 12. Histamine test meal: fasting secretion: quantity 8 cm<sup>3</sup>, free acid: 0, total acidity: 6. After  $\frac{1}{2}$  mg histamine-hydrochloride free acid was from 2 to 13. Total acidity: 17—39. Sedimentation rate: 6—1 mm. Platelets: 353,000. Osmotic resistance test: incipient hemolysis at 0.50 %, total at 0.36 %. Icteric index: 3. Colour index: 0.52—0.83. Halometry: 7.1  $\mu$ . Leucocytes: 6200—8700, of which neutrophile polymorphonucleated 66 %, red-nucleated 5 %, monocytes 4 %, lymphocytes 25 %. The percentage of reticulocytes, determined every other day, was constantly lower than 1 %. The other results are shown in Table 2 and visualized in diagram No. 1.

Table 2.

Days after hospital'n.	Hb. %	Red cor- puscles in millions	Serum ascorbic acid in mg %	Serum- iron in %	Treatment.
5	55	4.90	0.06	17	
8			0.67		
12	60	5.73	0.90	25	
15			1.02	16	← Ascorbic acid 0.10 × 3
19	50	4.20	0.99	38	
22			1.05		
26	55	4.38	0.81	36	
29			0.70	24	
33	58	5.31	0.58	21	ferri oxydum + saccharatum 0.75 × 3
36			0.93	14	
40	58	4.59	0.84	29	
43			0.38	25	
47	62	4.73	0.78	28	← Ascorbic acid 0.10 × 3
50	68	4.82	0.93	44	
54			0.73	49	
57			0.70	53	← Ferrous tartrate 0.50 × 3
61	70	4.23	0.64	59	
68	75	5.00	0.75	69	
82	80	5.64	0.52	97	
97	88	5.41	0.09	130	

**No. 2.** A. P. K. M. ♀, 25 years, unmarried shop assistant. Formerly well except that for several years had periodical, tardy, epigastric pains radiating out to the back, alleviated by eating; never hematemesis; never observed melena. Menses always regular. Consulted doctor for timitus, slight palpitation, headache tiredness.

**Physical examination:** Somewhat thin. Weight 48,5 kg, height 164 cm. Pale, not icteric. Hair growth natural. Tongue without papilla atrophy or pain, not tender. Remainder of physical examination completely normal, especially no oedema, heart normal. Temperature normal. Blood pressure: 115/90. Wassermann reaction negative. Ewald test meal (1 hour): 131 cm<sup>3</sup>, free acid: 56, total acidity: 90. Benzidine reaction on stools: negative (11 ×). Urine: nothing abnormal. X-ray of stomach: some hyper-secretion. On the greater curvature of the duodenal cap is a niche, over pea size; on the lesser curvature a shadow suspiciously like an ulcer. Sedimentation rate: on admission 28 mm, later 1 mm. Platelets 304,000. Osmotic resistance test: incipient haemolysis at 0,44 %, total at 0.30 %. Leucocytes 4500—11800, of which neutrophile polymorphonucleated 60 %, eosinophils 3 %, rod-nucleated 2 %, monocytes 9 %, lymphocytes 26 %. Colour index: 0,73—0,78, volumetric index:

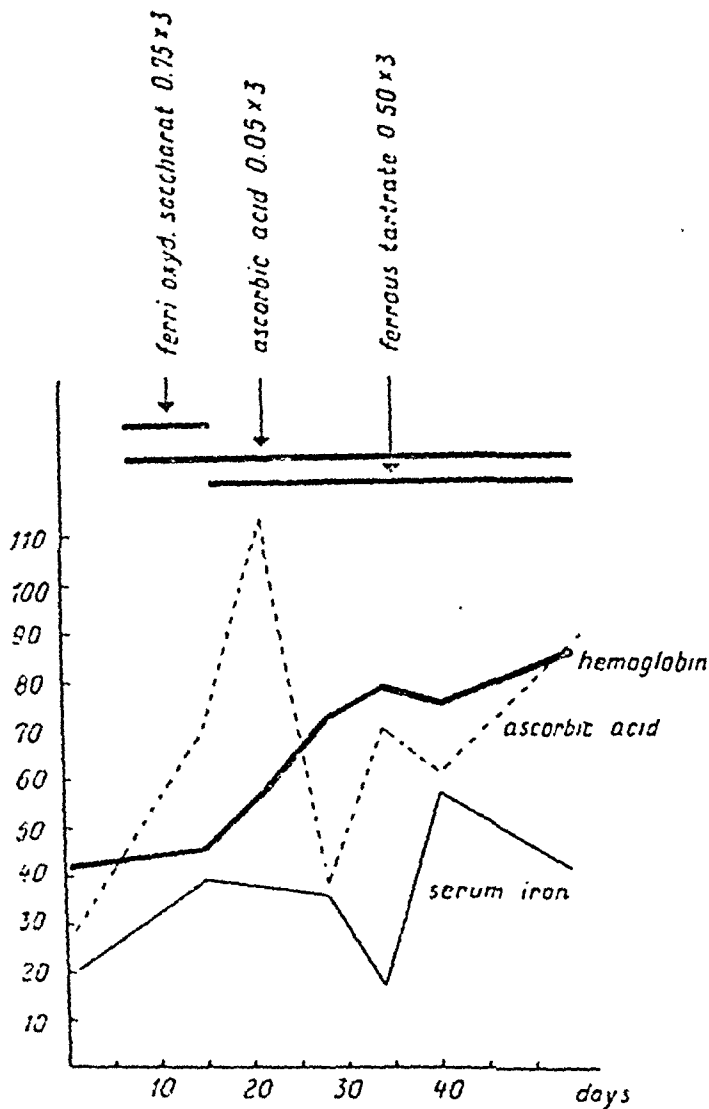


Diagram 2.

Table 3.

Days after hospital'n.	Hb %	Red corpuscles in millions	Serum ascorbic acid in mg %	Serum-iron in %	Treatment
1	42	2.89	0.29	20	ferri oxydum saccharatum 0.75 x 3
15	46	3.12	0.70	39	
21	57	3.66	1.13	138	
28	72	4.10	0.38	36	ascorbic acid 0.05 x 3
31	78	3.90	0.70	17	
40	75	5.00	0.61	57	
51	85	4.84	0.88	41	ferrous tartrate 0.50 x 3



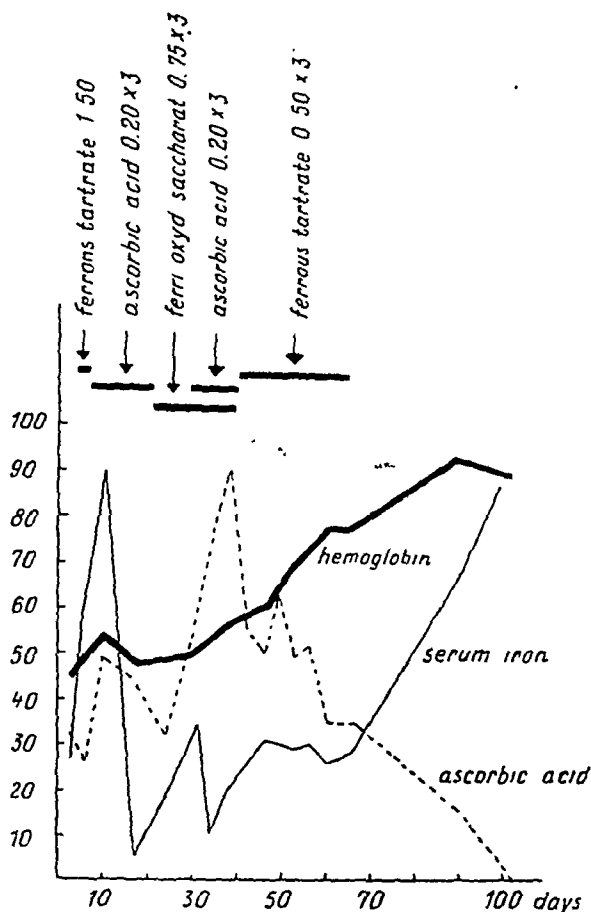


Diagram 3.

0.90, halometry: 7.1  $\mu$ . The other results are given in Table 3 and graphically in Diagram No. 2.

**No. 3.** K. C. P. ♀, 63 years, wife of cartman. When about 20 years old operated twice for hemorrhoids and hospitalized for gastric catarrh. At 55 years of age the patient had her uterus sewn up. One natural birth 25 years ago, menopause from 45th year, since when has been well generally except for some nervous restlessness, moderate sleep and an anxious mind, until a month prior to hospitalization she became tired and sleepy, felt the cold easily. Rhagades appeared at the corners of her mouth.

**Physical examination:** Well fed. Weight: 68,9 kg, height 159 cm. Rather pale, not icteric or cyanotic, no petechiae, grey haired. Rhagades at mouth corners. Some papilla atrophy, but the tongue not quite smooth. Complete upper and lower dentures. Nails slightly frayed. Heart: normal. Some pigmentation of the knees, but not the elbows. No oedema Temperature normal. Blood pressure: 165/80. Wassermann reaction negative. Urine: nothing abnormal. Ewald test meal (20 min.): 5 cm<sup>3</sup>, free acid: 0.

Table 4.

Days after hospital'n.	Hb. %	Red corpuscles in millions	Serum-ascorbic acid in mg %	Serum-iron in $\gamma$ %	Treatment
3	45	4.18	0.32	27	
6			0.26	63	← ferrous-tartrate 1.50
10	54	3.87	0.49	90	← ascorbic acid 0.20 $\times$ 3
17	48	4.47	0.44	5	
24	49	4.11	0.32	14	← ferri oxydum saccharatum 0.75 $\times$ 3
31	50	3.73	0.58	34	← ascorbic acid 0.20 $\times$ 3
34			0.75	10	
38	56	4.70	0.90	20	
42			0.55		
46	60	4.12	0.50	31	
49			0.64		
53	70	4.65	0.49	29	← ferrous tartrate 0.50 $\times$ 3
56			0.52	30	
60	77	5.07	0.35	26	
65	77	4.09	0.35	27	
90	93	5.49	0.15	67	
102	90	4.97	0.00	90	

total acidity: 12. Benzidine reaction on stools negative (12  $\times$ ). X-ray of stomach: gastroptosis, as in the erect position the incisura angularis is over three-fingers' width below the cristal line; otherwise normal. Sedimentation rate: 27—14 mm. Leucocytes: 3000—4700, of which neutrophil polymorphonucleated 54 %, eosinophils 2 %, rod-nucleated 3 %, monocytes 1 %. Lymphocytes 40 %. Colour index: on hospitalization 0.54 and on discharge 0.94. Other results shown in Table 4 and in diagram No. 3.

It will be seen from the curves and the tables that the effect of the treatment described a fairly parallel course in all three cases. After the ingestion of ascorbic acid there was, as might have been expected, a distinct rise of serum ascorbic acid without any simultaneous rise of serum-iron. The brief rise recorded by patient No. 3 round about the 10th day must be attributed to the fact that 1.5 g ferrous tartrate was given by mistake. The hemoglobin percentage remains unmoved, no matter whether the treatment is ascorbic acid, ferrisalt or both. It is only with the ingestion of ferrous tartrate that we observe a pronounced rise of the blood hemoglobin percentage, and at the same time there seems to occur a fall in the serum ascorbic acid (Nos. 1 and 3). However, Patient No. 1

was discharged from the Department on the 61st day, and she would scarcely afford to continue to take ascorbic acid. As regards Patient No. 3, she ceased taking ascorbic acid when she began with ferrous tartrate.

Thus it will be seen that in these three cases of anemia the ascorbic acid had no influence on the serum-iron level, neither when given alone nor when together with a ferri-compound. The first distinct increase is seen after the ingestion of ferrous tartrate. There is no doubt, however, that a marked increase of the serum-iron would have been found had there been an opportunity of continuing the tests.

### Conclusion.

A summing up of the results of our observations and investigations would be as follows: In the four cases of scurvy there were serum-iron values considerably below the normal; all these patients had simultaneously a moderately severe, normochromous or slightly hypochromous anemia, but one cannot venture to conclude from this that scurvy anemia is due to iron deficiency. The relatively high colour index and the protracted course of the anemia, despite the ingestion of iron, if anything argues against it; but as stated these cases permit of only limited conclusions being drawn.

In three patients with iron-deficiency anemia there were low values of both serum-iron and serum ascorbic acid in all cases, but from the experiments it seems clear that ascorbic acid plays no demonstrable role in the pathogenesis of these forms of anemia, as neither serum-iron nor blood values are affected by the ascorbic acid administered. Ferri-salts + ascorbic acid were likewise without effect; the first pronounced effect is secured by ferro-salts.

Thus the conclusion to be drawn from this investigation is a two-fold one, firstly that scurvy anemia is scarcely due to iron deficiency and is scarcely affected by administering iron, even if the low serum-iron values suggest an abnormal iron metabolism; secondly, that ascorbic acid has no influence on serum-iron and blood values in iron-deficiency anemia, though serum ascorbic acid in this state seems to be very low.

It must therefore be assumed that scurvy anemia and iron-deficiency anemia pathogenetically are two different states which present low serum-iron and serum-ascorbic acid values as a common clinical feature.

### Summary.

A description is given of four cases of classical scurvy with skin hemorrhage, muscular tenderness and anaemia; they are elderly men. In all cases there are low values for serum-iron and serum-ascorbic acid. After ingestion of ferrous tartrate and ascorbic acid the serum-ascorbic acid rises rapidly, but serum-iron and blood values only slowly. Two young women with chlorosis and an elderly woman with achylic anemia all have low serum-iron and serum-ascorbic acid values. After ingestion of ascorbic acid alone, and after ascorbic acid + ferri-salts, there is an increase of the ascorbic acid in serum but not of the serum-iron; this only increases after the ingestion of ferrosalt. From this it is concluded that even if the low values for serum-iron in scurvy indicate an abnormal iron metabolism, this disease is scarcely due to deficiency in iron. Conversely, ascorbic acid alone or ascorbic-acid + ferri-salt has no effect in simple iron-deficiency anemia, even if there are low values for serum-ascorbic acid in this disease too. It must therefore be assumed that scurvy anemia and iron-deficiency anemia pathogenetically are two different states which as a common clinical feature present low values for serum-iron and serum-ascorbic acid.

### Litterature.

Abt: J. A. M. A. 111: 17, 1941. — Faulkner: New Engl. J. Med. 19: 213, 1935. — Fraenkel, E.: Hdb. d. spez. Anat. u. Histol. v. Henke & Lubarsch. Bd. 9, 1. 222. Berlin 1929. — Hansmann: quoted by Abt. — Harris, H. A.: Quart. J. Med. 21: 499, 1928. — Heilmeyer, L. & Plötner, K.: Das Serumeisen und die Eisenmangelkrankheit. Fischer, Jena 1937. — Koch: Dtsch. Arch. Klin. Med. 185: 89, 1939. — Liu, Chu et al.: Proc. Soc. Experimen. Biol. & Med.: 44: 495, 1940. — Liu, Chu et al.: Proc. Soc. Experimen. Biol. & Med.: 46: 603, 1940. — Lorenz, E.: Arch. Kinderheilk.: 115: 129, 1938. — Lucksch, F.: Wien. klin. Wschr.: 53: 457, 1940. — Mettier, Minot & Townsend: J. A. M. A. 95, 1089, 1930. — Meulengracht, E.: Ugeskr. f. Læger 49: 165, 1927. — Parsons: Brit. Med. J.: 631, 1933. — Schmorl, G.: Jahrbuch f. Kinderheilk. 65: 50, 1907. — Schröder & Braun-Stappenbeck: Klin. Wschr. 20: 979, 1941. — Turnbull, H. M.: J. Path. Bact. 34: 277, 1931. — Turnbull, H. M.: J. Path. Bact. 35: 419, 1923. — Vahlquist, Bo Cson: Das Serumeisen. Thesis for doctorate. Uppsala 1941. — Wahren, H.: Klin. Wschr. 16: 1496, 1937. — Vaughan, J. M.: The Anaemias. Milford. London 1936. pp. 30 and 143.

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## Dissociation between Glomerular and Tubular Renal Function in Cases of Pyelonephritis.

By

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In his monograph »Hypertension and Nephritis» Fishberg (3) says that renal insufficiency is divisible into three groups: 1) glomerular, 2) tubular and 3) combined glomerular and tubular renal insufficiency, according to which elements of the kidney are particularly exposed to the pathological process and are functionally affected.

Glomerular renal insufficiency, which is characterized by reduced glomerulus filtration and retained tubulus resorption, excretion and synthesis, is diagnosed from oliguria, high spontaneous specific gravity, reduced inulin and kreatinine clearance, and normal values from the concentration test. Elective glomerular renal insufficiency occurs transitorily in glomerulonephritis acuta, in peripheral circulatory insufficiency and terminally in cardiac insufficiency.

Tubular renal insufficiency is characterized by reduced tubular resorption, synthesis and excretion as well as by preserved filtration. It is recognized by means of polyuria, reduced spontaneous specific gravity, normal inulin clearance and low values from the concentration test. This syndrome so far has been found only in Diabetes insipidus, whereas it has not hitherto been observed with any of the forms of Bright's disease or other kidney diseases.

Fishberg states that in Bright's disease, chronic pyelonephritis and other renal affections glomeruli and tubuli are influenced to the same degree, whereby combined glomerular-tubular renal insufficiency occurs. When one finds combined renal insufficiency in cases of glomerulonephritis chronica and amyloidosis renis, where one might have expected uncomplicated glomerular renal insufficiency, the reason may be that the blood supply to the tubuli suffers when glomeruli are injured, as the blood supplying the tubuli first passes the corresponding glomerulus.

On a number of patients with chronic nephritis and nephrosclerosis Holten & Rehberg (5, 6) made simultaneous concentration tests and filtration tests with kreatinine clearance. On the whole there was proportionality between these two renal function tests, and the authors conclude that the glomerular and tubular renal functions are reduced in fairly equal proportions by the advancing renal destruction caused by chronic nephritis.

By means of the current renal function tests — urea clearance and concentration test — it is possible to obtain an approximately correct expression of the glomerulus filtration and tubulus function. More exact values for these partial functions may be had by simultaneously determining the inulin clearance and  $T_m$  (the tubular excretory mass, which is expressed by the excretion of diodrast (mg diodrast-iodine per minute) in the urine at a high plasma-diodrast concentration) (11).

For some considerable time this Department has consistently made urea clearance and concentration tests on all patients suffering from pyelonephritis and pyelitis, a disease which, thanks especially to American authors [Longcope (8), Longcope & Winkler (9), and Weiss & Parker (12)] in recent years has attracted much more attention in the medical clinics than hitherto — not without reason, for undoubtedly it is one of the most frequent, if not the most frequent of all medical kidney affections.

In the course of these tests it has been observed that some of these patients with acute, sub-acute and chronic (often quite latent) pyelonephritis have a greatly reduced and sometimes completely abolished power of concentration, whereas the same patients have given normal values for urea clearance and blood urea.

To judge from the enormous quantity of literature on pyelonephritis, it would seem that this has not previously been noticed.

In 1936 Holten (4) reported on a case of hyperparathyreoidism with renal complications. This patient had a much reduced power of concentration and fairly well-preserved filtration (kreatinine clearance). Radiological examination of the kidneys revealed calcic accumulations corresponding to the medulla, which were assumed to have injured the cells of the tubuli electively.

Holten & Rehberg (5, 6) in 1931 saw two patients (Nos. 49 and 50) with chronic nephritis who had normal kreatinine clearance and reduced concentration; they assumed an isolated reduction of the tubulus function, but did not go into the cause of it. In the case reports of these two patients there is nothing to argue definitively against their having pyelonephritis; on the contrary, the former was a calculus patient and the other suffered from coliuria and dysuria.

Our own material will be described in the following:

#### 1) *Technique (7).*

*Urea clearance test* on all female patients was performed as a catheter clearance (at the commencement and conclusion of the clearance period vesica were completely emptied by catheter). With the males catheter clearance was performed by hypertrophia prostatae and strictura urethrae. The clearance period was one hour. The test was made in the morning on patients in bed and fasting — and usually two or three times.

Urea determination was according to van Slyke's urease method, which was frequently checked with known quantities of urea. All clearance values are calculated as the maximum clearance.

*Addis-Shevky's concentration test:* A dry diet was given from 8 am. til 10 am. next day (26 hours' thirst). The urine specific gravity was determined in two portions: from 8 pm. to 8 am. and from 8 am. to 10 am. Samples in which the first portion exceeded  $600\text{ cm}^3$  ( $25\text{ cm}^3$  per hour) and the second portion  $100\text{ cm}^3$  ( $50\text{ cm}^3$  per hour) were rejected. In some instances the patients thirsted only for 24 hours, and the specific gravity was determined for only one portion (from 8 pm. to 8 am.). The sp. gravity was determined by floating weight checked on distilled water at  $20^\circ$ , and by weighing.

During the tests the patients were in bed and under strict control. None of them had manifest edema. No correction was made for albuminuria, which in all patients was of negligible order.

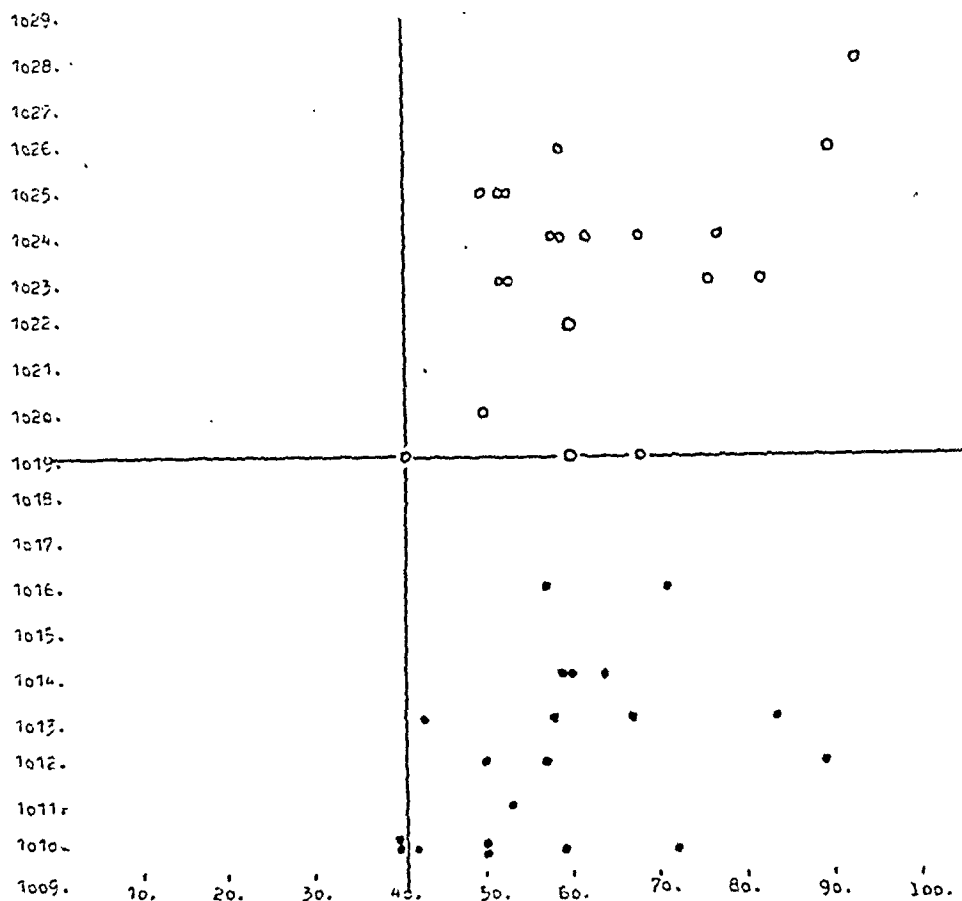


Fig. 1. Max. specific gravity and urea clearance (cc. per min.)  
 ○ normal subjects. ● pyelonephritis.

## 2) Control Material:

With this technique tests were made of 20 arbitrarily chosen patients who were not suffering from renal affections and never had done so, and who had normal urine analyses and blood pressure. The values found are shown in fig. 1. Accordingly, the lower limit for urea clearance and the concentration test was selected at: 41  $\text{cm}^3$  and specific gravity 1019. The same diagram contains the same function tests on the patients described below.

## 3) Extracts from Case Reports:

### *Pyelonephritis acuta.*

Case No. 1. ♀, 23 years, 805/42.

Pyelonephritis ac., Graviditas in M. V., Anaemia.

Not had pyelitis before. Acutely ill with cold shivers, temp. 40.6, pains in loins, dysuria, pollakisuria and turbid urine. Clearance: 1) (15 days



after beginning) 94 cm<sup>3</sup>. Diuresis/minute: 10 cm<sup>3</sup>, 2) (26 days after onset): 57 cm<sup>3</sup>. Diuresis/minute: 7 cm<sup>3</sup>. Concentration tests: 1) (18 days after onset): 8 pm.—8 am.: sp. gravity 1012 (410 cm<sup>3</sup>); 2) (28 days after onset): 8 pm.—8 am.: sp. gravity 1013 (240 cm<sup>3</sup>). Blood urea: 21 mg %. Blood pressure: 120/70. Urine: + albumin. Esbach: Traces. Microscopy: +++ leucocytes, + epithelial cells, +++ bacteria. Growth of B. coli.

Case No. 2. ♀, 19 years. 1589/42.

Pyelonephritis acuta, Graviditas in M. IV. Surditas.

No previous kidney affection. Acute pyelitis in fourth month with cold shivers, temp. 40, pains in loins and dysuria. Clearance: (11 days after onset): 57 cm<sup>3</sup>. Diuresis/minute: 6 cm<sup>3</sup>. Concentration test: (13 days after onset): 8 pm.—8 am.: sp. gravity: 1017 (560 cm<sup>3</sup>); 8—10 am.: sp. gravity: 1016 (100 cm<sup>3</sup>). Blood urea: 21 mg %. Blood pressure: 110/70. Urine: ÷ albumin. Esbach: 0. Mikroskopy: ++ leucocytes, + growth of Staph. aureus.

#### *Pyelonephritis subacuta — subchronica.*

Case No. 3. ♀, 27 years. 696/42.

Pyelonephritis subac.-subchron., Pneumonia, Anaemia, Emaciatio.

Acute pyelitis gravidarum 3 months prior to hospitalization, which since recurred. The kidney trouble no subjectively symptom-free. Clearance: 1) (2 ½ months after onset of pyelitis): 40 cm<sup>3</sup>. Diuresis/minute: 6.7 cm<sup>3</sup>. 2) (3 months after onset of pyelitis): 40 cm<sup>3</sup>. Diuresis/minute: 6.7 cm<sup>3</sup>. Concentration tests: 1) (2 ½ months after onset) 8 pm.—8 am.: sp. gravity 1010 (400 cm<sup>3</sup>); 2) (3 months after onset): 8 pm.—8 am.: sp. gravity 1010 (640 cm<sup>3</sup>). Blood urea: 30 mg %. Blood pressure: 120/70. Urine: + albumin. Microscopy: +++ leucocytes. Growth of B. coli. Esbach: 0.4 ‰.

#### *Pyelonephritis chronica (latent stage).*

Case No. 4. ♀, 67 years. 1256/42.

Pyelonephritis chron., Bronchitis chron., Anaemia, Degeneratio myocardii.

Had pyelitis 15 years ago, for which confined to bed in periods for a year. Now subjectively symptom-free. Otherwise no record of renal affection. Clearance: 59 cm<sup>3</sup>. Diuresis/minute: 5.4 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1010 (400 cm<sup>3</sup>). Blood urea: 14 mg %. Blood pressure 170/95—125/70. Urine: + — 0 albumin. Microscopy: + — 0 leucocytes. Growth of B. coli.

Case No. 5. ♀, 73 years. 1105/42.

Pyelonephritis chron., Anaemia perniciosa, Myelopathia anaemica, Hypertonia 1 gr, Degeneratio myocardii.

Knows nothing of earlier renal affection; has suffered much from «lumbago». Clearance: 50 cm<sup>3</sup>. Diuresis/minute: 4.3 cm<sup>3</sup>. Concentration test:

8 pm.—8 am.: 1012 (200 cm<sup>3</sup>). Blood urea: 19 mg %. Blood pressure: 185/95—150/80. Urine: + — 0 albumin. Esbach: 0. Microscopy: +++ leucocytes. Growth of *B. coli*.

Case No. 6. ♂, 45 years. 331/42.

Stricture urethrae, Cystopyelonephritis chron., Hepatitis ac.

Gonorrhoea when 25 years old. During last seven years symptoms of stricture and chronic cystitis. Ignorant of any kidney trouble. Clearance: 71 cm<sup>3</sup>. Diuresis/minute: 7.7 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity: 1016 (560 cm<sup>3</sup>). Blood urea: 21 mg %. Blood pressure: 150/90—120/80. Urine: +++ leucocytes. +, +, +, 0 albumin. Esbach: 0.2 ‰. Growth of *Staph. aureus*. X-ray of kidneys: No trace of concretions.

Case No. 7. ♂, 65 years. 900/42

Pyelonephritis chron., Stricture urethrae antea. Spondylitis deformans, Arteriosclerosis, Degeneratio myocardii.

In 1937 treated for Stricture urethrae with dilatation; now symptom-free. Ignorant of any renal affection. Clearance: 1) 50 cm<sup>3</sup>. Diuresis/minute: 8 cm<sup>3</sup>; 2) 37 cm<sup>3</sup>. Diuresis/minute: 7 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity 1010 (560 cm<sup>3</sup>); 2) 8 pm.—8 am.: sp. gravity: 1009 (550 cm<sup>3</sup>). Blood urea: 25 mg %. Blood pressure: 185/105—145/80. Urine: + albumin. Microscopy: +++ leucocytes, ++ epithelial cells. Growth of *B. coli*. Ophthalmoscopy: nothing abnormal. Intravenous pyelography: nothing abnormal.

Case No. 8. ♀, 73 years. 707/42.

Edema pulm.. Bundle Branch Block, Pyelonephritis chron., Anaemia.

Never had pyelitis or other kidney trouble. Hospitalized for edema pulm. Clearance: 1) 58 cm<sup>3</sup>. Diuresis/minute: 4.8 cm<sup>3</sup>; 2) 32 cm<sup>3</sup>. Diuresis minute: 3.5 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1013 (460 cm<sup>3</sup>). Blood urea: 24—32 mg %. Blood pressure: 165/90—130/65. Urine: + albumin. Esbach: 0.5 ‰. Microscopy: +++ leucocytes, +++ bacilli. Growth of *B. coli*. Pyelography: Slow excretion on right side. Pelvis and calyces slightly dilated on left side.

Case No. 9. ♂, 73 years. 1394/42.

Pyelonephritis chron., Emaciatio, Senilitas.

Pains in the loins since 35th year. Three or four times passed small stones in urine. When 62 years hospitalized for cystopyelitis. No trouble with urinary passages since. Clearance (catheter): 1) 50 cm<sup>3</sup>. Diuresis/minute: 3.7 cm<sup>3</sup>. 2) 41 cm<sup>3</sup>. Diuresis/minute: 6 cm<sup>3</sup>. 3) 35 cm<sup>3</sup>. Diuresis/minute: 7.3 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity: 1014 (500 cm<sup>3</sup>). 2) 8 pm.—8 am.: sp. gravity: 1009 (440 cm<sup>3</sup>). Blood urea: 35 mg %. Blood pressure: 150/80—120/60. Urine: + — 0 albumin. Esbach: 0. Microscopy: + — +++ leucocytes. +++ bacilli. 0 cylinders or erythrocytes. Growth of *B. coli* and *faecalis alkaligenes*. Intravenous. Pyelography: nothing abnormal.

*Pyelonephritis chronica (manifest stage).*

Case No. 10. ♀, 42 years. 868/42.

Pyelonephritis chron., Nephrolithiasis dext. Hydronephrosis sin. 1 g. Renal colic on both sides since her 16th year. Excretion of calculi, haematuria, dysuria, and turbid urine. Clearance: 83 cm<sup>3</sup>. Diuresis/minute: 9.3 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1013 (580 cm<sup>3</sup>). Blood urea: 21 mg %. Blood pressure: 120/70. Urine: + albumin. Esbach: 0.3 ‰. Microscopy: +++ erythrocytes, ++ leucocytes, ++ epithelial cells; growth of non-haemolytic streptococci. X-ray of kidneys: two concretions on right side. On left side pelvis is enlarged with slightly dilated calyces.

Case No. 11. ♀, 27 years. 1367/40.

Pyelonephritis chron., Hypertonia, Hypertrophia cordis, Retinopathia hypertonica, Encephalopathia hypertonica.

In 1934 acute pyelitis, which later recurred with fever and loin pains. About 1939—40 hypertension developed with rapidly progressing retinopathia hypertonica. A number of convulsions, followed by coma. Subsequently died on October 1941 under uraemia and hemiplegia. Autopsy: Uraemia, Pyelonephritis chron. bilateralis, Hypertrophia cordis ventr. sin. Clearance: 1) 89 cm<sup>3</sup>. Diuresis/minute: 5 cm<sup>3</sup>; 2) 51 cm<sup>3</sup>. Diuresis/minute: 3 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1012 (550 cm<sup>3</sup>). Blood urea: 22 mg %. Blood pressure: 215/145—165/120. Urine: + — 0 albumin. Esbach: 0. Microscopy: + — ++ leucocytes, 0 — + growth of B. coli. Ophthalmoscopy: exudates, haemorrhages and papillary edema. Intravenous pyelography: Calyces on right side enlarged.

Case No. 12. ♀, 44 years. 1287/41.

Nephrolithiasis sin., Pyelonephritis chron., Abscessus perirenalis, Mb. cordis mitralis.

Coral stone in the left kidney diagnosed in 1936. Since then had pains in left loin, haematuria, frequent and painful urination. Hospitalized with acute pyelitis and signs of perirenal abscess on the left side as well as Pleuropneumonia sin. Nephrectomia sin. was performed. Diagnosis: Nephrolithiasis, Pyelonephritis subac.-subchron. mg. g. cum ulceratione. Clearance: 1) 67 cm<sup>3</sup>. Diuresis/minute: 7.3 cm<sup>3</sup>; 2) 67 cm<sup>3</sup>. Diuresis/minute: 7 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1013 (480 cm<sup>3</sup>). Blood urea: 24 mg %. Blood pressure: 140/75. Urine: + albumin. Microscopy: ++ erythrocytes, ++ leucocytes; growth of B. proteus and coli.

Case No. 13. ♀, 61 years. 774/42.

Calculus renis sin., Hydronephrosis sin., Pyelonephritis chron., Carc. uteri seq.

In Rigshospital 1914 for nephrolithiasis. In Kommune Hospital 5th Dept. in 1941 for renal calculus pains on left side. Pyelography: Calculus renis sin., Hydronephrosis sin. No excretion of contrast on right side.

Clearance: 42 cm<sup>3</sup>. Diuresis/minute: 6 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1010 (240 cm<sup>3</sup>). Blood urea: 23 mg %. Blood pressure 160/110—135/80. Urine: + — 0 albumin. Microscopy: +++ leucocytes. Growth of *B. coli*.

Case No. 14. ♀, 29 years. 1485/42.

Pyelonephritis chron. duplex. Epilepsia.

At 19 years Nephropathia gravidarum; afterwards slight duplex loin pains, pyuria, haematuria, albuminuria and headache. Clearance: 1) 35 cm<sup>3</sup>. Diuresis/minute: 7.5 cm<sup>3</sup>; 2) 60 cm<sup>3</sup>. Diuresis/minute: 11 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity 1012 (580 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1014 (60 cm<sup>3</sup>); 2) 8 pm.—8 am.: sp. gravity 1012 (620 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1012 (130 cm<sup>3</sup>). Blood urea 32 mg %. Blood pressure 120/80—155/90. Urine: + albumin. Esbach: 0.3—0.5 ‰. Microscopy: + leucocytes, ++ epithelial cells. Growth of *B. coli*. Pyelography: No excretion of contrast on right side; dilatation of calyces on left side.

Case No. 15. ♂, 74 years. 1581/42.

Pyelonephritis acuta in chronica, Glomerulonephritis antea, Hypertrophia prostatae, Resectionis prostatae seq., Cystitis, Anaemia.

In 1893 acute nephritis (glomerulo-?). During last 25 years hypertrophia prostatae. Twice electro-resected. Last half year repeated acute pyelitis. Clearance: 1) 63 cm<sup>3</sup>. Diuresis/minute: 3.5 cm<sup>3</sup>; 2) 50 cm<sup>3</sup>. Diuresis/minute: 7 cm<sup>3</sup>; 3) 40 cm<sup>3</sup>. Diuresis/minute: 2.3 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1011 (560 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1014 (80 cm<sup>3</sup>). Blood urea: 27 mg %. Blood pressure: 140/80. Urine: + albumin. Esbach: 0.1—0.3 ‰. Microscopy: +++ leucocytes, +++ bact. Growth of *B. coli*. Pyelography: large, deformed pyelograms. Cystoscopy: Cystitis, Hypertrophia prostatae.

Case No. 16. ♂, 67 years. 1241/42.

Hydronephroses duplex, Diabetes mellitus, Emaciatio, Observatio.

Ignorant of any kidney affection. Hospitalized owing to loss of weight and pains in abdomen. Clearance: 72 cm<sup>3</sup>. Diuresis/minute: 2.6 cm<sup>3</sup>. Concentration test: 8 pm.—8 am.: sp. gravity 1010 (310 cm<sup>3</sup>). Blood urea: 32 mg %. Blood pressure: 130/80. Urine: + albumin. Esbach: trace. No growth. Microscopy: Nothing abnormal. Pyelography: duplex large hydronephrosis — of unknown pathogenesis.

Case No. 17. ♀, 60 years. 1534/42.

Pyelonephritis chron., Hypertonia 1 gr.

When a child had nephritis; since then almost always had periods with loin pains, dysuria, fever and turbid urine. When pregnant had edema. Clearance: 1) 39 cm<sup>3</sup>. Diuresis/minute: 6.6 cm<sup>3</sup>; 2) 59 cm<sup>3</sup>. Diuresis/minute: 9 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity 1015 (375 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1014 (77 cm<sup>3</sup>). 2) 8 pm.—8 am.: sp. gravity 1015 (380 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1013 (90 cm<sup>3</sup>). Blood

urea: 42—25 mg %. Blood pressure: 170/90—135/80. Urine: 0 albumin (numerous analyses). Microscopy: ++ leucocytes. +++ Bact. Growth of *B. coli*. Intravenous pyelography: nothing abnormal.

Case No. 18. ♀, 61 years. 1588/41.

Pyelonephritis chron. duplex, Hypertonia.

Pyelitis in 1926; symptom-free till 1939; since then dysuria, attacks of pain in both kidney regions, the right especially, intermittently febrile, macroscopic haematuria, foul, turbid urine. Clearance: 1) 34 cm<sup>3</sup>. Diuresis/minute: 1.5 cm<sup>3</sup> 2) 40 cm<sup>3</sup>. Diuresis/minute: 1.7 cm<sup>3</sup>. Concentration tests 1) 8 pm.—8 am.: sp. gravity 1008 (500 cm<sup>3</sup>). 2) 8 pm.—8 am.: sp. gravity 1010 (460 cm<sup>3</sup>). 3) 8 pm.—8 am.: sp. gravity 1011 (510 cm<sup>3</sup>); 8 am.—10 am.: sp. gravity 1010 (155 cm<sup>3</sup>). 4) 8 pm.—8 am.: sp. gravity 1011 (480 cm<sup>3</sup>) 8 am.—10 am.: sp. gravity 1010 (125 cm<sup>3</sup>). Blood urea: 25 mg %. Blood pressure: 200/110—120/80. Urine: + — 0 albumin. Esbach: 0. Microscopy: +++ — 0 erythrocytes. +++ leucocytes. 0 casts. + epithelial cells. Growth of *B. coli*. Intravenous pyelography: Pelves dilated. Clubbing and irregular dilatation of calyces. Ureters slightly dilated.

*Nephritis chronica (suspected Pyelonephritis).*

Case No. 19. ♀, 19 years. 1627/43.

Nephritis chron. (Pyelonephritis chron.?), Tonsillitis chron.

Often had colds and sore throat. During past six months suffered from tiredness, headache, loss of appetite and pain across the loins. Never acute pyelitis or acute glomerulonephritis. The day prior to hospitalization turbid urine, dysuria and albuminuria. While in hospital pains and tenderness in right kidney region. Clearance: 1) 43 cm<sup>3</sup>. Diuresis/minute: 4.3 cm<sup>3</sup>. 2) 43 cm<sup>3</sup>. Diuresis/minute: 5.3 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity 1017 (410 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1011 (90 cm<sup>3</sup>). 2) 8 pm.—8 am.: sp. gravity 1013 (470 cm<sup>3</sup>). 8 am.—10 am.: sp. gravity 1012 (110 cm<sup>3</sup>). Blood urea: 45—33 mg %. Blood pressure: 130/75. Urine: ++ albumin. Esbach: 0.4—1 ‰. Microscopy: + — 0 leucocytes. 0 erythrocytes. 0 leucocytes. 0 casts. + — epithelial cells. No growth. Bing's bead test: 6.2 %. Pyelography: Nothing abnormal. Throat examination: Tonsillitis chron. Ophthalmoscopy: natural.

Case No. 20. ♀, 65 years. 1317/41.

Nephritis chron., (Obs. pro Pyelonephritis chron.) Ulcus duodeni.

No acute renal affection. Since 1933 albuminuria and pain across the loins. No fever, haematuria, passing of stones, pollakisuria or dysuria. Clearance: 1) 53 cm<sup>3</sup>. Diuresis/minute: 4.8 cm<sup>3</sup>. 2) 40 cm<sup>3</sup>. Diuresis/minute: 3 cm<sup>3</sup>. Concentration tests: 1) 8 pm.—8 am.: sp. gravity 1010 (300 cm<sup>3</sup>). 2) 8 pm.—8 am.: sp. gravity 1011 (248 cm<sup>3</sup>). Blood urea: 39 mg %. Blood pressure: 170/100—130/80. Urine: ++ albumin. Esbach: 1—2.5 ‰. Microscopy: + — ++ leucocytes. + casts. + epithelial cells. No bact. Growth of *B. coli*. Ophthalmoscopy: natural. Pyelography: R. pyelogram indistinct.

## Discussion.

These case reports form the basis for the postulate that in some cases of pyelonephritis there is a dissociation between the glomerular and the tubular renal functions. It may be argued against the theory that the urea clearance is not so explicit a measure of the glomerulus function as the concentration test is of the tubulus function; about 40 per cent. of the urea filtered in glomeruli is resorbed and may diffuse back from tubuli, so that a tubular affection must also to some extent influence the urea clearance (10). However, the urea clearance provides a useful idea as to the glomerulus function, as usually it is proportional to glomerulus filtration (1, 2).

This dissociation between glomerular and tubular function conforms well with the current opinion as to the canalicular distribution of pyelonephritis in the kidney. It is presumable that in its initial stage and well into the chronic stage pyelonephritis attacks the tubular apparatus either in its entirety or predilectively, and only very much later — if at all — attacks glomeruli. This is also confirmed by the slight albuminuria that is so characteristic of pyelonephritis chronica and in certain cases (cf. Cases No. 4, 5, 6, 9, 11, 13 and 18) periodically disappears, and in others (cf. Case No. 17) is entirely absent.

Weiss & Parker (12) hold that acute pyelitis very often, and perhaps in every case, patholo-anatomically is pyelonephritis. Cases No. 1 and 2 are evidence that acute pyelitis may involve functional tubular renal insufficiency at a very early stage; it should be stated, however, that we have seen many cases of acute pyelitis where the renal function was unaffected, and only a single case in which acute pyelitis progressed to death in uraemia.

The true clinical importance of the observation would seem to lie in the fact that it will be of assistance in the often very difficult differential diagnosis of the chronic kidney inflammations (Pyelonephritis chron., Glomerulonephritis chron., Nephrosclerosis). Even if this is chiefly academic in character, it is of significance if for example it is desired to define the prognosis of the individual renal affection. It will appear from the case reports that dissociation between clearance and concentration test was observed in only two patients (Nos. 19 and 20), in respect of whom the diagnosis of pyelonephritis could not be made definitely from other diag-

nostic criteria (anamnesis, X-ray finds, urine finds). Though we feel fairly well convinced of the importance of dissociation to this diagnosis, we have provisionally elected to call it *Nephritis chronica* with a suspicion of pyelonephritis.

In four patients (Nos. 3, 8, 11 and 15) there was a tendency towards a high diuresis (1.5—2.5 litres) — i. e. very little polyuria, whereas the diuresis of the others was normal. It is rather surprising that this tendency towards polyuria was not more strongly marked, having regard to the usually very poor concentration demonstrated; according to Holten & Rehberg (5, 6) however, hypo- and isostenuria are not nearly always accompanied by polyuria, which is generally found only when there is N-retention.

According to Holten & Rehberg (5, 6) there can be no elective, tubular affection unless the glomerulus filtration is simultaneously reduced; the inhibited resorption of water will increase the pressure in the capsular space and thus reduce the conditions for glomerulus filtration. Our observations seem to contradict this statement (as already stated, Holten & Rehberg themselves found certain cases of dissociation between clearance (kreatinine) and concentration test), and it is possible that an increase of the capsular pressure is not reflected so much in reduced tubular function as has been imagined.

For the purpose of obtaining further confirmation of this dissociation between glomerulus and tubulus function in pyelonephritis by means of more exact figures it is intended to elucidate the problem further by means of clearance determinations with inulin and diodrast (Perabrodil).

### Summary.

In some cases of acute pyelitis and a number of cases of chronic pyelonephritis the author demonstrates a dissociation between the tubulus function (which is found by the concentration test to be much reduced) and the glomerulus function (which the urea clearance proved to be wholly or almost wholly normal). The observation seems to indicate renal functions that are characteristic of pyelonephritis and its long chronic, more or less latent stage and may be used in making the differential diagnosis of chronic nephritis.

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## Die Ausscheidung des Bilirubins im Harn und ihre Abhängigkeit vom Serumbilirubin.

Von

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(Bei der Redaktion am 27. April 1943 eingegangen).

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Die Ausscheidung des Bilirubins im Harn und deren Abhängigkeit vom Bilirubingehalt des Serums sind wohl bisher zwar schon Gegenstand mehrerer Untersuchungen gewesen, aber im Verhältniss zu den zahlreichen Arbeiten über das Serumbilirubin, gibt es doch erstaunlich wenige Arbeiten über die Bilirubinausscheidung im Harn. Da diese Arbeiten ausserdem grösstenteils mit älteren, nicht ganz zuverlässigen Analysemethoden durchgeführt sind und an mehreren Punkten strittig sind, kann man eine erneute Untersuchung dieser Fragen mit zuverlässigeren Analysemethoden für angezeigt ansehen.

### Frühere Untersuchungen.

In der Literatur findet man allgemein angegeben, dass Bilirubinurie nur dann gefunden wird, wenn die Diazoreaktion im Serum eine direkte ist; das »indirekte« Bilirubin wird nicht als »harnfähig« angesehen (vgl. McNee, Bensley, Faltitschek u. Hess). Diese Auffassung wird allgemein v. d. Bergh zugeschrieben, aber mit Unrecht, da er in keiner seiner Arbeiten (1918, 1921, 1924) eine solche Anschauung ausspricht; ja, er berichtet im Gegenteil (1918,

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<sup>1</sup> Die Untersuchungen sind mit Unterstützung von P. Carl Petersens Fond durchgeführt.

S. 59) über einen Fall von hämolytischem Ikterus (also indirekte Diazoreaktion), der vorübergehende Bilirubinurie zeigte. Diese Auffassung scheint von McNee (1923) zuerst formuliert, später in der Literatur als Tatsache hingenommen und niemals bezweifelt worden zu sein.

Weiter fand v. d. Bergh (1918), dass Bilirubinurie bei einer Serumkonzentration von etwa 2 mg pro 100 ml auftritt, und dass dieser Schwellenwert recht konstant zu liegen scheint. Spätere Untersuchungen mit v. d. Bergh's Methode — die übrigens von v. d. Bergh selbst (1924) keineswegs als einwandfrei aufgefasst wurde — ergaben zu ähnliche Ergebnisse. Es ist hier von Bedeutung sich klar zu machen, dass »indirektes« Bilirubin bei der Alkoholfällung in weit geringerem Umfang als »direktes« an den Proteinniederschlag adsorbiert wird (v. d. Bergh, 1918, 1921, 1924), was eine höhere Serumbilirubinkonzentration für »indirekt« als für »direkt« reagierenden Bilirubin bewirkt, wenn die Bilirubinkonzentration tatsächlich die gleiche ist. Dieser Umstand kann ganz unmittelbar den Befund höherer Schwellenwerte der Harnausscheidung für »indirektes« Bilirubin als für »direktes« erklären, wenn die Bestimmungen nach v. d. Bergh's Methode durchgeführt sind. Diese natürliche Erklärung für den höheren Schwellenwert des indirekten Bilirubins scheint bisher übersehen worden zu sein.

Später sind diese Fragen von Zeit zu Zeit in der Literatur berührt worden. Schiff u. Eliasberg (1922) teilte Untersuchungen über eine Hepatitis-epidemie bei Schulkindern mit; etwa die Hälfte der Fälle zeigte direkte Reaktion im Serum, die übrigen indirekte; es konnte kein klinischer Unterschied zwischen ihnen nachgewiesen werden, und die Bilirubinurie zeigte auch ganz ähnliche Verhältnisse in den beiden Gruppen. Dieselben Verfasser teilen einen Fall von Occlusionsikterus (congenite Gallenwegsatrechie) mit, bei welchem starker Ikterus und ausgesprochene Bilirubinurie von indirekter Diazoreaktion des Serums begleitet waren.

Faltitschek u. Hess (1936) berichten über drei Fälle von ausgesprochenem Ikterus mit direkter Diazoreaktion im Serum und Totalbilirubin zwischen 7 und 20 mg pro 100 ml aber ohne Bilirubinurie. Da eine ernste Niereninsuffizienz in allen drei Fällen vorlag, muss man annehmen, dass Bilirubin bei beschädigter Nierenfunktion schwierig oder gar nicht ausgeschieden wird; *der Schwellenwert muss also in einem gewissen Masse von der Nierenfunktion abhängig sein.* Dies wird auch durch die Untersuchungen Bennhold's (1932) nahegelegt; dieser Verfasser wies darauf hin, dass das Serumbilirubin stets an Serumalbumin gebunden ist, weil Harnbilirubin frei ist, und er nahm an, dass die Niere an der Auskoppelung der Bilirubin-Albumin-Verbindung aktiv beteiligt war.

Dass der Schwellenwert eine nicht unbeträchtliche Variation zeigen kann, wurde von Andrewes (1924) und Retzlaff (1923) gefunden. Meulengracht (1920) fand den Schwellenwert bei Ikterusindex 40—50, was nach den Untersuchungen With's (1942, 1943) etwa 3 bis 8 mg Bilirubin pro 100 ml entspricht. Die Bedeutung der direkten Reaktion für die Harnausscheidung wurde von Bensley (1933) untersucht; er bestimmte die direkte und indirekte Reaktion des Serums mit v. d. Bergh's Methode und das Harnbilirubin mit Hunter's (1930) Diazomethode, die im wesentlichen mit der in unseren Untersuchungen benutzten Methode übereinstimmt. Er liess die Patienten ein Paar Stunden vor der Blutprobe urinieren, und der kurz nach der Blutprobe gelassene Harn wurde untersucht. Die Resultate werden für Serum und Harn schätzungsweise als »schwache Spuren«, »Spuren« und »deutliche Reaktion« angegeben; nur Fälle mit Serumwerten unter 2 mg pro 100 ml (4 v. d. Bergh-Einheiten) wurden untersucht, da die Ausscheidung bei höheren Werten als sicher betrachtet wurde. Die Untersuchungen an diesen schwachen Ikterusgraden zeigten keine Korrelation zwischen der Harnausscheidung und der totalen Diazoreaktion des Serums, während eine gewisse Korrelation zwischen der Harnausscheidung und der direkten Reaktion nachweisbar war, die aber all zu wenig ausgesprochen war um den Namen direkter Abhängigkeit zu verdienen. Weiter wurden 5 Fälle mit direkter Reaktion ohne Bilirubinurie und 4 Fälle mit indirekter Reaktion (1—5 v. d. Bergh-Einheiten) und schwache Bilirubinurie beobachtet.

Rabinowitch (1932) verwendete dieselben Analysemethoden wie Bensley, er konnte aber Bilirubinurie in 30 % der Fälle mit normalen Serumbilirubinwerten nachweisen, und ist der Ansicht, dass Bilirubin auch bei Normalen im Harn vorkommt, aber in den meisten Fällen in so kleinen Mengen, dass mit den üblichen Untersuchungsmethoden nicht nachweisbar sei.

Riesel (1939) ist der einzige, der bisher eigentlich quantitative Untersuchungen von Serum und Harn miteinander verglichen hat; er benutzte Serumanalysen nach der Salzsäuremethode nach Heilmeyer (1938) und Harnanalysen nach einer von ihm selber ausgearbeiteten, auf demselben Prinzip basierten Methode (der Harn wurde mit  $\text{BaCl}_2$  gefällt; konz.  $\text{HCl}$  wurde als Reagenz benutzt, und die Farbe kolorimetrisch gemessen). Er konnte deutlicher Unterschied zwischen der Ausscheidung in Fällen von parenchymatösem Ikterus (10 Fälle untersucht) und Fällen von Okklusionsikterus (9 Fälle) nachweisen; seine Ergebnisse werden als Säulendiagramm hergestellt, aus welchen hervorgeht, dass die Bilirubinkonzentration im Harn, in Prozent des Serumbilirubins ausgedrückt, bei parenchymatösem Ikterus nur 10—30 % war, während sie bei 8 von 9 Fällen von Okklusionsikterus 90 %, oder mehr war; in dem letzten Fall von Okklusionsikterus war sie jedoch nur 40 %. Mann kan leider nur das Verhältniss zwischen Serum- und Harnwerte nicht aber die absolute Grösse der Werte dem Diagramm entnehmen.

Schliesslich soll noch bemerkt werden, dass Ylppö (1913) meinte, kleine Bilirubinmengen im Harn von Kindern mit Ikterus neonatorum (von

der Grösse ca. 0.10 mg pro Tag) nachweisen zu können, und dass Ross, Waug und Malloy (1937) meinten, bei ikterischen Neugeborenen kleine Bilirubinmengen im Harn nachweisen zu können (0.008 mg pro 100 ml), während sie bei nichtikterischen Neugeborenen keine Bilirubinurie fanden.

### Eigene Analysemethoden.

Wie oben besprochen, muss man den Grund der fehlenden Übereinstimmung zwischen den Ergebnissen der verschiedenen Untersuchungen in den Analysemethoden suchen. Für Serum hat man allerdings jetzt eine spezifische und quantitative Methode, die ausserdem sehr einfach ist, nämlich Jendrassik und Gróf's (1938); diese Methode kann ausserdem leicht als Mikromethode mit Kutanblut benutzt werden [With (1), 1942, 1943] und, mit einzelnen Modifikationen [With (1), 1943] auch für quantitative Messung der direkten Reaktion.

Die Vorgangsweise bei der Messung der direkten Reaktion besteht darin, dass man destilliertes Wasser statt der Koffeinelösung — sowohl in der Reaktionslösung als der Kontrollösung — verwendet. Das neue an dieser Methode ist, dass man nicht wie sonst bei Messungen der direkten Reaktion im Serum die rote Farbe des neutralen Azobilirubins, sondern die blaue Farbe des alkalischen Azobilirubins misst. Hierbei ist es möglich, eine stabile Farbe abzulesen, da der Reaktionsprozess der Diazoreaktion beim Alkalisieren sofort abgebrochen wird, während man bei der Messung in neutraler Lösung eine Farbe, die nicht stabil, sondern zunehmend ist, zu messen hat. Ein weiterer Vorteil dieser Methode (With, 1943) ist, dass die blaue Farbe des alkalischen Azobilirubins gegen die gelbe Farbe des nicht-diazotierten Bilirubins besser sichtbar ist, als die rote Farbe des neutralen Azobilirubins; dieses Verhältniss tritt besonders deutlich hervor bei schwachen direkten Reaktionen, die bei neutraler Reaktion überhaupt nicht unmittelbar sichtbar sind, während sie nach Alkalizusatz deutlich hervorgehen.

In unseren Untersuchungen wurde das Alkali (Fehlings Flüssigkeit B) 30 Sekunden nach der Zumischung der Diazoreagenz zugesetzt (z. B. 0.1 ml Serum + 0.2 ml H<sub>2</sub>O + 0.05 ml Diazomischung + 0.15 ml »Fehling«; als Kontrollösung wurde dieselbe Mischung nur mit der gleichen Menge 15 % Salzsäure statt Diazomischung benutzt). Wir wählten diese Vorgangsweise, da man ja allgemein die gewöhnliche, direkte van den Bergh-Reaktion etwa 30 Sekunden nach der Diazotierung abzulesen pflegt (vgl. z. B. Bensley). Die Ergebnisse der direkten Reaktion werden wie für das Totalbilirubin in mg pro 100 ml umgerechnet; man muss jedoch berücksichtigen, dass man bei der Berechnung von der von dem Koffein herführende Korrektur absehen muss.

Die Harnanalysen wurden nach der Methode von Jendrassik und Gróf (1938) für Harn vorgenommen. Diese Methode ist als

spezifisch und quantitativ anzusehen mit Ausnahme von Fällen mit gleichzeitigem Vorkommen von grösseren Urobilinmengen [With, (2), 1942].

Da der Harn in sämtlichen hier besprochenen Fällen auf Urobilinstoffe untersucht wurde (Methode nach With, 2, 1942) und sich hierbei entweder als ganz urobilinfrei oder wenigstens nur kleine Urobilinmengen enthaltend zeigte, kann man ganz von dieser Fehlerquelle absehen. Übrigens ist es leicht zu kontrollieren, wenn die Methode einmal versagt, da man in solchen Fällen statt der reinen roten Farbe des Azobilirubins, die nach dem Salzsäurezusatz in Blau übergeht, andere gelbliche Farbtöne findet. Diese Methode ist der obengenannten Methode von Hunter sehr ähnlich (abgesehen davon, dass man dabei das neutrale Azobilirubin statt des alkalischen bestimmt, und nicht im Pulfrichfotometer abliest, sind die zwei Methoden praktisch identisch), und wird von Foord und Baisinger (1940) als die empfindlichste Methode für Harn aufgefasst; eine weitere Verbesserung ergibt sich jedoch, wenn man die Ausfällung in derselben Weise vornimmt, aber die Diazotierung auf einem weissen Filter, auf welchem der Niederschlag durch Filtrierung aufgefangen ist, durchführte (sogenannte »Diazo-Spot-Methode«). Wir haben diese »Diazo-Spot-Methode« in Fällen, wo die Methode nach Jendrassik und Gróf unsichere Ergebnisse leistete gebraucht und hierdurch mehrmals Spuren von Bilirubin nachweisen können.

### Eigene Untersuchungen.

Da die Bilirubinkonzentration des Serums sich nur langsam ändert, abgesehen von speziellen Gelegenheiten (z. B. bei dem Abgang eines Gallensteins), haben wir die Bilirubinkonzentration des frisch gelassenen Harns mit der Bilirubinkonzentration einer gleichzeitig genommenen Serumprobe verglichen, indem wir jedoch die Patienten die Harnblase ein bis zwei Stunden vor der Probenahme entleeren liessen und die Blutprobe in dem Intervall zwischen den zwei Miktionen oder kurz nach der letzten nahmen. Die Harnanalysen wurden innerhalb einer Stunde nach dem Harnen durchgeführt, und die Harnproben bis zur Analyse im Eisschrank aufbewahrt.

Wir haben die Tagesvariation des Serumbilirubins beim Ikterus an 5 Hepatitispatienten mit Ikterus verschiedenen Grades untersucht; diese Patienten wurden dreimal täglich untersucht in Perioden ohne klinisch nachweisbare Veränderungen im Krankheitsprozess; die Ergebnisse der Analysen gehen aus Tabelle 1 hervor. Gegen Variationen des Serumbilirubins verursacht durch Änderungen im Krankheitsprozess haben wir uns dadurch gesichert,

dass wir in allen den untersuchten Fällen tägliche Bestimmungen des Serumbilirubins durchführten in den gleichen Perioden, in denen wir das Harnbilirubin untersuchten. Im Diagramm haben wir nur solche Werte angeführt, bei welchen das Serumbilirubin sowohl am Versuchstage als am vorhergehenden und folgenden Tage ungefähr dasselbe Niveau aufwies (d. h. Variationen innerhalb  $\pm 10\%$  des Mittelwerts der 3 Bestimmungen).

Tabelle 1.

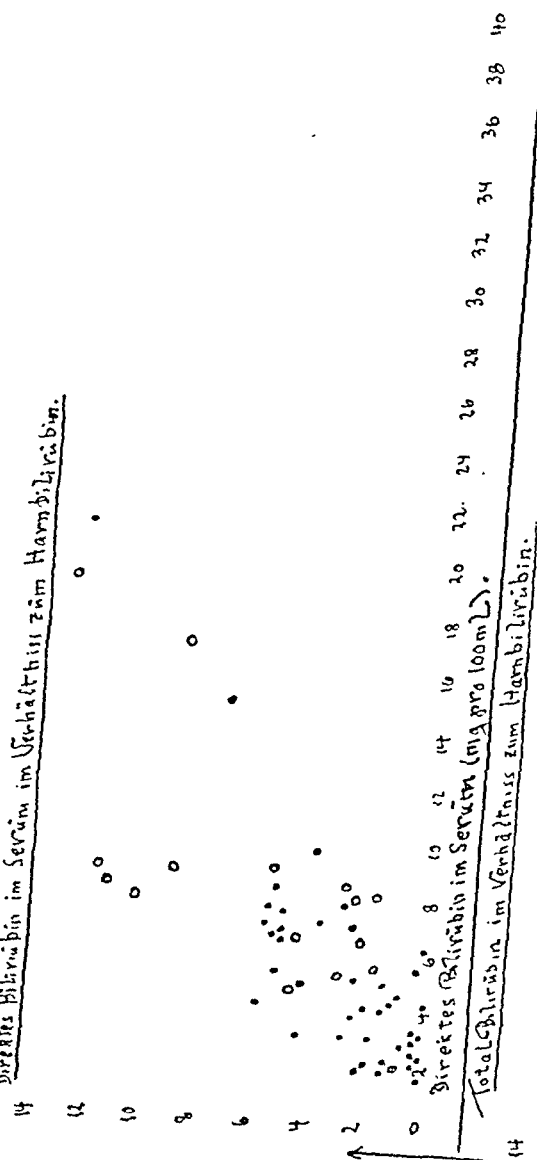
*Die Variationen des Serumbilirubins beim Ikterus (Hepatitis acuta).*

	9 Uhr	12 Uhr	18 Uhr	9 Uhr (am folgenden Tage)
Pat. Nr. 1	4.43	4.01	4.05	3.85 mg pr. 100 ml.
Pat. Nr. 2	4.96	4.82	4.58	4.81 " " "
Pat. Nr. 3	12.6	11.4	11.0	13.0 " " "
Pat. Nr. 4	29.5	28.0	27.3	30.3 " " "
Pat. Nr. 5	3.41	3.20	3.52	3.83 " " "

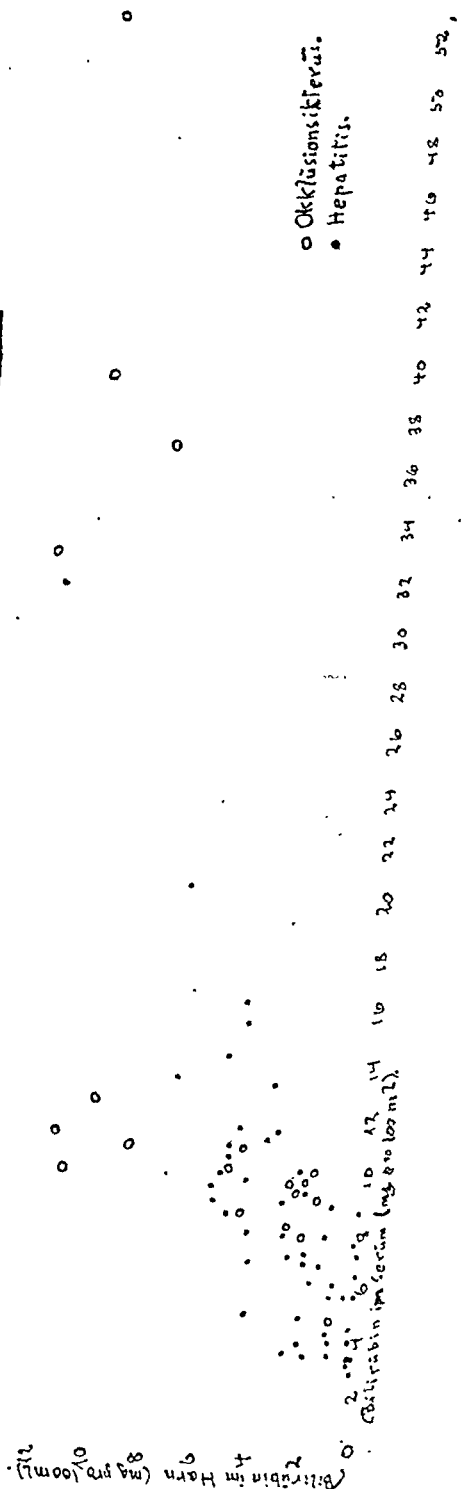
Es geht aus der Tabelle hervor, dass die Variation des Serumbilirubins innerhalb 24 Stunden etwa 10 % beträgt, dass aber der Unterschied zwischen dem höchsten und niedrigsten Wert stets unter 20 % des Mittelwerts liegt. Die Werte bei 9 Uhr sind nüchtern bestimmt die übrigen Werte vor der Mittags- respektive Abendmahlzeit.

Die Tagesvariationen des Serumbilirubins bei normalen Personen sind früher von Bröchner-Mortensen und Huhtala eingehend untersucht worden. Diese Verfasser fanden beide, dass die Werte am häufigsten nach Mahlzeiten abnahmen, und dass die Variationen, in absoluten Zahlen gemessen, klein waren (am häufigsten nur einige Zehntel mg pro 100 ml) obwohl sie in manchen Fällen beträchtlichen Prozentteilen des vorhandenen Wertes entsprachen (bis zur 30 % nach Bröchner-Mortensen). Grössere Variationen — Steigerung des Wertes mit 100 bis 300 % — können durch länger dauernde Fasten (22 bis 36 Stunden) und besonders durch mit Muskelarbeit kombinierte Fasten verursacht werden (Huhtala). Ob man hierdurch auch stärkere Steigerungen des Serumbilirubins bei Ikteruskranken verursachen kann, scheint noch nicht untersucht zu sein, da aber solche Umstände bei den von uns untersuchten Patienten nicht eintrafen, kann man ruhig die in der obengenannten Weise bestimmten Serum- und Harnwerte mit einander vergleichen, da die Serumkonzentration sich in den 2 der Harnausscheidung entsprechenden Stunden nicht bedeutend verändert haben kann.

Direktes Bilirubin im Serum im Verhältnis zum Hamobilirubin.



Bilirubin im Harn (mg pro 100 ml)



○ Okklusionsikterus.  
● Hepatitis.

### *Erläuterung zum Diagramm 1.*

Unsere Ergebnisse sind im Diagramm dargestellt. Der untere Teil des Diagramms zeigt das Totalbilirubin in Beziehung zum Harnbilirubin, während der obere Teil die Beziehung zwischen Harnbilirubin und der direkten Reaktion zeigt. Die Harnwerte sind an der vertikalen Achse abgesetzt die Serumwerte an der horizontalen; alle Werte sind in mg pro 100 ml gegeben. Die Hepatitisfälle sind mit massiven Punkten, die Fälle mit Okklusionsikterus mit dem Zeichen 0 bezeichnet. »Spuren« im Harn sind mit Zeichen an der Nulllinie und fehlende Reaktion im Harne mit Zeichen unter der Nulllinie bezeichnet. Es wurden 23 Hepatitisfälle und 9 Patienten mit Okklusionsikterus untersucht.

### **Der Schwellenwert für die Ausscheidung des Bilirubins im Harn.**

Es geht aus Diagramm 1 hervor, dass der Schwellenwert eine beträchtliche Variation zeigt. Er liegt gewöhnlich zwischen 3 und 6 mg Totalbilirubin pro 100 ml, und bei Werten unter 3 mg pro 100 ml wurde Bilirubinurie niemals gefunden. Bei Werten zwischen 3 und 4 mg pro 100 ml wurde Bilirubinurie in einem einzigen Fall gefunden (bei mehreren Untersuchungen), bei Werten zwischen 5 und 6 mg pro 100 ml fast regelmässig; zwischen 6 und 9 mg pro 100 ml Serum fehlte Bilirubinurie in einzelnen Fällen von Hepatitis, während dies bei Okklusionsikterus nicht der Fall war; da wir aber nur 9 Fälle mit Okklusionsikterus untersuchten, kann man nicht auf Grund unseres Material schliessen, dass der Schwellenwert bei Okklusionsikterus sich anders verhält als bei Hepatitis.

### **Das Verhältniss zwischen der Bilirubinkonzentration im Serum und Harn.**

Wie es aus Diagramm 1 sehr deutlich hervorgeht, kann es keine lineare Korrelation zwischen der Bilirubinkonzentration des Serums und des Harns geben. Z. B. entsprechen in einem Fall



von Okklusionsikterus ca. 10 mg pro 100 ml in Serum ca. 2 mg pro 100 ml im Harn, während in einem anderen Fall derselben Serumkonzentration etwa 11 mg pro 100 ml Harn entsprechen. So grosse Streuung ist jedoch nicht die Regel, und wenn man nur mit den Werten des einzelnen Falls rechnet, wird die Streuung ganz natürlich weit kleiner als, wenn man sämtliche Fälle zusammen betrachtet. Doch kann man auch innerhalb der Werte des einzelnen Falles beträchtliche Variationen konstatieren; z. B. fanden wir in einem Fall von Hepatitis bei Serumbilirubin von etwa 3.5 mg pro 100 ml Harnwerte zwischen 0.8 und 2.6 mg pro 100 ml.

Trotz aller Variationen besteht jedoch die *Hauptregel*, dass die *Harnkonzentration zwischen 25 und 50 % der Serumkonzentration liegt*, welches man sehr einfach dadurch kontrollieren kann, wenn man die Linien mit den Gleichungen  $y = x/4$  und  $y = x/3$  in das Diagramm zeichnet. Es gibt jedoch Ausnahmen von dieser Regel, da Prozente zwischen 15 und 75 vorkommen, und in einem einzelnen Fall von langdauerndem Okklusionsikterus (bei cancer pankreatis) sogar Werte von 100 % und etwas darüber. Wir konnten aber keine sicheren Unterschiede in der Bilirubinausscheidung zwischen Okklusionsikterus und Hepatitis nachweisen, wenn man von dem genannten einzelnen Fall von cancer pankreatis absieht. In einem Fall von Okklusionsikterus mit sehr hohem Serumwerte war die Harnausscheidung sogar als Prozent gerechnet verhältnismässig niedrig (bei mehreren Bestimmungen etwa 25 %). Wir konnten also die obenbesprochene Auffassung Riesel's über einen charakteristischen Unterschied in der Ausscheidung zwischen Okklusionsikterus und parenchymatösem Ikterus nicht bestätigen.

Die Verhältnisse bei *Ikterus neonatorum* sollen noch erwähnt werden, da sie eine Sonderstellung einnehmen. Wir haben in Zusammenarbeit mit E. Hj. Larsen Harn und Serum von 20 Neugeborenen mit mehr oder weniger ausgesprochenen Ikterus Neonatorum sowie 1 Fall von Ikterus gravis neonatorum (starker Ikterus und schwere Anämie) untersucht. Hierbei wurde *Bilirubinurie nur bei Werten über 18 mg pro 100 ml Serum gefunden*, und die beobachteten Harnkonzentrationen machten nur ein Par Prozent des Serumwerts aus (es wurde nur Bilirubinurie in zwei von den 20 Fällen gefunden; der eine Fall zeigte 0.72 mg pro 100 ml im Harn und 31.0 ml im Serum und später respektive 0.11 und 18.5 mg pro 100 ml, der andere Spuren im Harn und 19.6 ml in Serum). Der

Fall von Ikterus gravis zeigte einem niedrigeren Schwellenwert, aber jedoch eine niedrige Ausscheidung im Prozent des Serumwerts (0.30 mg pro 100 ml Harn bei 14.7 mg pro 100 ml Serum und später respektive 0.20 und 8.3 mg pro 100 ml).

*Der Schwellenwert des Serumbilirubins für die Bilirubinausscheidung im Harn beträgt also bei Erwachsenen nur etwa ein Drittel wie bei Neugeborenen; die Ursache dieses Verhältnisses ist wahrscheinlich eine physiologische Niereninsuffizienz bei Neugeborenen (vgl. McCance und Young, 1940). Wie man erklären soll, dass mehrere Verfasser Bilirubinurie als gewöhnliche Erscheinung bei Ikterus neonatorum gefunden haben (vgl. oben) können wir nicht sagen; es ist doch bemerkenswert, dass die von diesen Verfassern angegebenen Bilirubinkonzentrationen so gering sind, dass sie unserer Meinung nach ausserhalb der Grenzen sicherer Erkenntniss liegen; dasselbe ist übrigens mit dem Befund von Bilirubin im Harn bei normaler Serumbilirubinkonzentration der Fall (vgl. Rabinowitch's Beobachtungen oben). Es kann weiter angeführt werden, dass der Harn in den meisten Fällen von Ikterus neonatorum ganz klar und hellgelb war; die seltenen Fällen mit Bilirubinurie zeigten deutlich dunklere Harnfarbe.*

### Die Bedeutung der direkten Diazoreaktion des Serums.

Wie aus Diagramm 1 hervorgeht, zeigt die direkte Diazoreaktion des Serums etwa dieselbe Streuung in ihrem Verhältniss zum Harnbilirubin wie das Totalbilirubin. Natürlich betragen die Harnwerte hier ein beträchtlich höherer Prozentsatz, als das bei dem Totalbilirubin der Fall ist (zwischen 50 und 100 % der Serumwerte). Gäbe es einen festeren Zusammenhang zwischen Harnausscheidung und direkter Reaktion, würde man bedeutend weniger ausgesprochene Streuung in der oberen Hälfte des Diagramms (direkte Reaktion) als in der unteren (Totalbilirubin) erwarten dürfen, aber ein solcher Unterschied ist nicht sichtbar. Unsere Untersuchungen sprechen also gegen einen festeren Zusammenhang zwischen der direkten Serumreaktion und der Ausscheidung des Bilirubins im Harn.

## Über den Mangel an Bilirubinurie bei hämolytischem Ikterus.

Der Mangel an Bilirubinurie bei Ikterus hämolytischen Ursprungs ist eine der wichtigsten Stützen der Theorie über die fehlende Harnfähigkeit des indirekten Bilirubins. Man hat aber, so weit wir sehen können, bisher die Möglichkeit übersehen, dass dieser Mangel an Bilirubinurie ganz einfach durch niedrige Serumkonzentrationen bei hämolytischen Ikterusformen verursacht sein könne, eine Möglichkeit, die um so grösser ist, wenn man bedenkt, dass v. d. Bergh nachweisen konnte, dass das »direkte« Bilirubin weit stärker am Eiweissniederschlag adsorbiert wird als das »indirekte« bei hämolytischen Ikterusformen vorkommende (vgl. oben). Die Untersucher, die beim hämolytischen Ikterus Serumwerte über dem Schwellenwert gefunden haben, haben alle die Ursprüngliche v. d. Bergh-Technik benutzt, die teils ernste Nachteile aufweist und teils für indirektes Bilirubin höhere Werte ergibt als für direktes; diese Untersuchungen können also die mangelnde Harnfähigkeit des indirekten Bilirubins nicht beweisen.

Grösserer Interesse haben in diesem Zusammenhang Untersuchungen, die auf direkten Kolorimetrie der gelben Farbe des Serumbilirubins gegründet sind (z. B. Untersuchungen mit dem sogenannten Ikterusindex), da die von der Eiweissfüllung herührenden Fehler hier nicht im Betracht kommen. Solche Untersuchungen über hämolytischen Ikterus sind von Meulengracht und Watson durchgeführt worden.

Meulengracht (1920) gibt an, etwa 40 Patienten mit hämolytischem Ikterus untersucht zu haben, und dass er hierbei einen Ikterisindex zwischen 3 und 41, in der Regel 10—20 gefunden hat. Ausführlichere Erläuterungen über seine Untersuchungen findet man in seiner Monographie (1918) über den hämolytischen Ikterus. Wenn man die Krankengeschichten durchsieht, ergibt sich, dass nur 14 Fälle von hämolytischem Ikterus mit Ikterusindex untersucht wurden, von welchen nur zwei Werte über 40 (Obs. 23: 41 und später 54 und Obs. 25: 48) und 5 Fälle Werte über 20 aufwiesen. In keinem Fall wurde Bilirubinurie gefunden.

Watson (1937, S. 215) berichtet über Untersuchung von 12 Fällen mit zahlreichen Einzelbestimmungen. Der Ikterusindex wurde nicht wie von Meulengracht angegeben mit Verdünnungskolorimetrie, sondern im Autenrieths Kolorimeter im Vergleich mit Meulengrachts Bichromat-Farbenstandardlösung abgelesen (in Meulengrachts oben besprochenen Untersuchungen wurden aber nicht mit diesem Standard, sondern mit

einem Pikrinsäurestandard verglichen). Watson fand etwas höhere Indexwerte als Meulengracht nämlich 8 bis 94; nur zweimal wurden Indexwerte über 40, nur 9 mal über 32 gefunden. Es werden keine Erläuterungen über Bilirubinurie gegeben.

Nach Untersuchungen von With (1942; Tabelle 3 und 4) ist das Verhältniss zwischen Ikterusindex und Serumbilirubin in mg pro 100 ml gemessen (nach Jendrassik und Grófs Methode bestimmt) etwa 5: 1 für hohe Indexwerte, während man für Indexwerte von 10—40 6: 1 bis 10: 1 findet. Hieraus kann man berechnen, dass Indexwerten unter 40 nur ausnahmsweise Serumbilirubinwerte über 6 mg pro 100 ml entsprechen, und in den meisten Fällen sogar Werte unter 4 mg pro 100 ml. Es scheint also, nach diesen mit nicht geeigneter Technik durchgeführten Untersuchungen zu urteilen, so zu sein, dass die meisten Fälle von hämolytischem Ikterus unter dem von uns gefundenen Schwellenwert für Bilirubinurie liegen (vgl. oben), dass man aber bei dieser Ikterusform doch gelegentlich Serumwerte finden kann, die in dem Schwellenwertgebiet 3 bis 6 mg pro 100 ml liegen. Wie häufig solche Werte gefunden werden, kann man aber nur durch Untersuchen mit geeigneten Analysemethoden finden.

Selbst haben wir 5 Fälle hämolytischer Ikterusformen untersucht. Ein Fall von hereditären hämolytischem Ikterus zeigte bei drei Bestimmungen 6.12, 4.84 und 3.16 mg pro 100 ml, ein anderer 1.60 und ein dritter 2.76. Ein Fall von Schwarzwasserfieber<sup>1</sup> nach therapeutischer Malaria (im Stadium der akuten Hämolyse untersucht) zeigte 2.52 und eine Patientin mit frischer unbehandelter Perniciosa zeigt 2.57 mg pro 100 ml. Diese Ergebnisse bestätigen, dass man bei hämolytischen Ikterusformen nur ausnahmsweise Serumbilirubinwerte über 4 mg pro 100 ml findet, und es ist deshalb nicht so verwunderlich, dass man bei diesen Ikterusformen keine Bilirubinurie findet, dass man sich hierbei zur Aufstellung einer Hypothese über »mangelnde Harnfähigkeit« des indirekten Bilirubins gezwungen sehen sollte. Eine ganz ähnliche Anschauung kann man übrigens aus der Arbeit Meulengracht's (1920) lesen, indem er einen Schwellenwert für Bilirubinurie bei Ikterusindex 40—50 (niedrigster Wert 36) fand und — wie oben besprochen — nur ganz ausnahmsweise Indexwerte über 40 bei hämolytischen Ikterusformen.

Es dürfte also an der Zeit sein, die so allgemein anerkannte, aber so schlecht dokumentierte Hypothese über die mangelnde Harnfähigkeit des indirekten Bilirubin fallen zu lassen, da alle Ergebnisse sich ohne diese Hypothese ganz natürlich erklären lassen.

<sup>1</sup> Von M. Faber und J. Boas, Nord. Med. 1942: 16: 3538 veröffentlicht.

## Über Variationen in der Bilirubinausscheidung mit Harn.

Man hat angeführt, dass der Schwellenwert für Bilirubinurie ein anderer sein solle, wenn das Serumbilirubin steigt. Über diese Frage können wir nicht aus eigener Erfahrung sprechen, da wir keine Gelegenheit dazu gehabt haben den Schwellenwert bei ansteigendem Serumbilirubin (z. B. Beispiel im Beginn einer Hepatitis) zu bestimmen. Wir haben aber gefunden, dass es bei demselben Fall bedeutende Variationen in der Harnausscheidung ohne korrespondierende Variationen im Serumbilirubin geben kann; z. B. gibt es oft beträchtliche Unterschiede in der Bilirubinkonzentration zwischen verschiedenen Harnportionen innerhalb derselben 24-Stundenperiode, ohne dass man parallele Variationen im Serumbilirubin nachweisen kann (vgl. oben).

Aus den zahlreichen Beispielen sollen hier nur einige Hepatitisfälle besprochen werden, in denen wir genaue tägliche Beobachtungen über das Serumbilirubin sowie über Bilirubinkonzentration im Harn und Diurese in Perioden von 3 bis 16 Stunden vornahmen. Alle Bilirubinwerte sind in mg pro 100 ml.

*Beispiel 1:* Serumbilirubin 24/2 (am 9 Uhr, nüchtern) 9.43; Harn zwischen 12 Uhr und 15 Uhr gesammelt; Diurese 230 ml, Bilirubinwert 5.64; hieraus wird der »Clearance«-Wert (Harnkonzentration  $\times$  Diurese pro Min. mit dem Serumkonzentration dividiert) 0.80 berechnet. Am 26/2 wurde im Serum 10.4 gefunden; Harn 8 Uhr bis 12 Uhr 230 ml mit Bilirubin 2.57 und 12 Uhr bis 15 Uhr 190 ml mit Bilirubin 2.26; »Clearance«-Werte. 0.25 und 0.23.

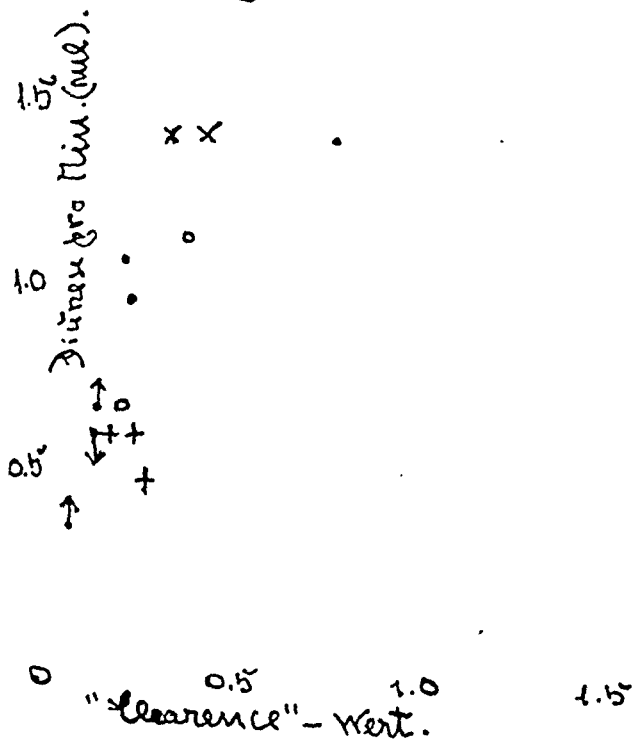
*Beispiel 2:* 23/1 Serum 3.62; Harn 8 Uhr bis 12 Uhr 150 ml und 1.36, »Clearance« 0.24. — 24/1 Serum 5.42; Harn 12 Uhr (23/1) bis 8 Uhr (24/1) 1200 ml und 2.14; »Clearance« 0.40; Harn 8 Uhr bis 12 Uhr 30 ml war frei von Bilirubin; dass dieser Fall der Harnbilirubinkonzentration von einem Fall des Serumbilirubins begleitet sein sollte, ist sehr unwahrscheinlich, da Serumwerte zwischen 3.16 und 4.23 in den Tagen 27/1 bis 29/1 gefunden wurden.

*Beispiel 3:* 22/1 Serum 3.90; Harn 8 Uhr bis 12 Uhr 330 ml und 1.00 und 12 Uhr bis 15 Uhr 250 ml und 1.28; »Clearance« 0.36 und 0.45. 24/1 stieg das Serumbilirubin wieder an — es war ein Fall akuter Hepatitis, der ein Par Wochen gedauert hatte — und zeigte den Wert 9 um 9 Uhr, und 8.61 um 12 Uhr; im Harn 8 Uhr bis 12 Uhr (245 ml) wurde kein Bilirubin gefunden. Es ist zu bemerken, dass die Bilirubinurie in den zwischenliegenden Tagen stufenweise abnahm; wir haben aber in diesen Tagen keine Serumbestimmungen vorgenommen.

Tabelle 2.

»Clearance«-Werte für Bilirubin.

Beispiel No.	Observation No.	Serumbilirubin (mg pro 100 ml)	Harnbilirubin (mg pro 100 ml)	Diurese (ml pro Min.)	»Clearance«
1	1	9.43	5.64	1.38	0.80
1	2	10.4	2.57	0.96	0.25
1	3	10.4	2.26	1.06	0.23
2	1	3.62	1.36	0.66	0.24
2	2	5.42	1.11	2.14	0.40
3	1	3.90	1.00	1.38	0.36
3	2	3.90	1.28	1.40	0.45
4	1	6.76	4.08	0.47	0.30
4	2	6.16	2.90	0.58	0.27
4	3	6.16	2.20	0.58	0.20
5	1	7.10	1.80	0.66	0.17
5	2	7.10	1.76	0.33	0.09
6	1	9.40—10.4	3.04	0.58	0.17

Diagramm 2.

*Beispiel 4:* 7/11 Serum 6.76, 8/11 Serum 6.16; Harn 16 Uhr (7/11) bis 8 Uhr (8/11) 450 ml und 4.08; »Clearance« ca. 0.30; 8 Uhr bis 12 Uhr 140 ml und 2.90; »Clearance« 0.27; 12 Uhr bis 16 Uhr 140 und 2.20; »Clearance« 0.20.

*Beispiel 5:* 19/2 Serum 7.10; Harn 8 Uhr bis 12 Uhr 160 ml und 1.80; »Clearance« 0.17; 12 Uhr bis 15 Uhr 60 ml und 1.76; »Clearance« 0.09.

*Beispiel 6:* 6/4 um 9 Uhr Serum 10.4 mg pro 100 ml; um 12 Uhr 9.40 mg pro 100 ml. Harn 9 Uhr bis 12 Uhr 105 ml und 3.40 mg pro 100 ml; »Clearance« 0.17.

Wir haben die Ergebnisse dieser 6 Beispiele in Tabelle 2 und Diagramm 2 zusammengefasst.

Aus Diagramm 2 geht ein gewisser Zusammenhang zwischen Diurese pro Minute und »Clearance«-Wert hervor, indem im allgemeinen eine grössere Diurese pro Minute einer grösseren »Clearance«-Wert zu entsprechen scheint.

Man kann sich diese Befunde nicht in anderer Weise erklären als durch die Annahme, dass die Ausscheidung des Bilirubins im Harn nur teilweise vom Bilirubingehalt des Serums bestimmt wird, und dass *andere Faktoren als die Bilirubinkonzentration des Serums eine entscheidende Rolle für die Bilirubinkonzentration des Harns spielen*. Die grosse Streuung der Punkte des Diagramms 1 bietet eine weitere Stütze für diese Annahme.

### Zusammenfassung.

Die Literatur wird besprochen; Untersuchungen mit zuverlässigen Analysemethoden sind erforderlich. Es wird über Serum- und Urinuntersuchungen mit Jendrassik und Gróf's Methode in 23 Hepatitisfälle und 9 Fälle von Okklusionsikterus berichtet. Weiter werden Serumbestimmungen in 5 Fällen von hämolytischem Ikterus sowie Untersuchungen über die Tagesvariation des Serumbilirubins in 5 Hepatitisfällen vorgelegt.

Der Schwellenwert für Bilirubinurie variierte zwischen 3 und 9, am häufigsten 3—6 mg pro 100 ml. Für Ikterus neonatorum betrug er doch 18 mg pro 100 ml. Es wurde im Harn 15—75 %, am häufigsten 25—50 % der im Serum vorgefundenen Konzentration beobachtet; nur in einem Fall (cancer pankreatis) wurden Werte von ca. 100 % beobachtet. Es bestand kein sicherer Unterschied zwischen Okklusionsikterus und parenchymatösem Ikterus. Bei Ikterus neonatorum wurde im Harn nur ein Par Prozent der Serumkonzentration vorgefunden.

Die direkte Reaktion wird besprochen; sie kann keine Bedeutung für die Bilirubinausscheidung im Harn haben. Die Hypothese über die fehlende Harnfähigkeit des indirekten Bilirubins wird diskutiert und als überflüssig und ungenügend begründet gefunden.

Bilirubin scheint nicht eine Schwellenwertsubstanz im eigentlichen Sinne zu sein, da andere Faktoren als die Serumkonzentration entscheidende Bedeutung für die Ausscheidung im Harn haben müssen.

### Literatur.

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## **Chronic Polyarthritis and Trauma.**

By

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The etiology of rheumatic diseases is still far from being clearly settled in spite of the intensive research that has taken place, especially during the last decades, in this branch of medicine. In fact, it is still an open question, whether acute and chronic polyarthritis can be attributed to the same cause. While from a pathologico-anatomical point of view, we may perhaps most readily assert with Klinge, that the essential character of all forms of »rheumatism» is an altered immuno-biological condition, many clinicians consider that both acute and chronic polyarthritis are mainly due to specific infections.

Setting aside these two conceptions of etiology, it then appears that general agreement has been reached concerning the existence of certain causative factors, which give the clinical aspect of polyarthritis its special character. Among many other contributing factors are traumata.

The problem of the relationship between trauma and polyarthritis is an old one. Brugière, in his dissertation of 1817, was the first to approach this problem. During the nineteenth century there appeared a number of treatises on this subject, first by French and then by German authors. The great majority of these publications dealt with acute polyarthritis as a result of traumata; but a few were more comprehensive and treated the problem of trauma-polyarthritis in its entirety.

In his »Thèse de Paris», (1912), Deveau wrote:

Il nous suffit de savoir qu'il y a un rhumatisme succédant à un trauma, que la preuve n'est pas fournie d'une manière, mais que les faits assez nombreux pour exclure tout de coïncidence et admettre une relation de cause à effet suffisant pour la pratique.

Since then notices of further cases have been published. In Scandinavia, Edström has described five cases of acute polyarthritis as a result of trauma. To judge by this, it would appear that the concurrence of trauma and subsequent polyarthritis is not considered to be due to mere chance. Consequently, we find agreement among clinicians who have studied the question, that trauma can cause acute polyarthritis.

On the other hand, this is far from being the case when it is a question of the primary chronic form. There are comparatively few works that only treat of the significance of trauma in the genesis of chronic polyarthritis. In Scandinavian literature Engström has dealt with the question, and later, von Koch has interested himself in cases of sub-chronic and chronic polyarthritis. Quite recently, in a series of articles on polyarthritis, Edström has dealt with the problem: trauma-polyarthritis, and has published some cases which he considers illustrate the part played by trauma even in chronic polyarthritis.

It would naturally have been easier to estimate the role played by trauma, if the etiology of polyarthritis had been determined. Since this is not the case, we have to depend entirely on direct clinical observations. These are as yet insufficient for us to adopt a definite standpoint. There are some who deny that trauma has any etiological significance, and they are apparently not in a minority. For instance, Krebs, who distinguishes between primary and secondary chronic polyarthritis, states that he has never seen a single case of primary chronic polyarthritis which was definitely caused by trauma. But he also states that one cannot get away from the fact that a causal relation does exist.

F. Coste (1937) treats of traumatic diseases of the joints. He writes very cautiously concerning chronic polyarthritis (polyarthrite chronique évolutive), that some cases are known where the incipience of polyarthritis coincides with trauma; but adds, that these cases are rare. If the problem of chronic traumatic polyarthritis is to be solved in a positive manner, a wider range of data will

have to be furnished, which demonstrate convincingly the possibility of a causal connection.

When it is a matter of establishing a causal relation between trauma and acute polyarthritis, where the conditions are perhaps simpler than in the case of chronic polyarthritis, the following conditions have been suggested as necessary, in order to determine that trauma has been the cause of polyarthritis.

1) The time interval between the trauma and the polyarthritis should be as short as possible.

2) The symptoms, in the joint which has been affected by trauma, should not have completely disappeared before the arthritic alterations appear in other joints not affected by the trauma. That is to say, before the process becomes a polyarthritic diffusion.

3) Polyarthritis is to commence in the injured joint.

But concerning the last condition (3), there is lack of unanimity. Some of the authors are of the opinion that trauma may be looked upon as having caused acute polyarthritis, even if the latter did not begin in the injured joint.

When attempting to set up similar conditions for the relationship between trauma and chronic polyarthritis, we must take into account the difference in the development of acute and chronic polyarthritis. It is true that we do not know any definite incubation period for acute polyarthritis. According to clinical experience however, this should be reckoned rather in days than weeks; and from this point of view, it is held that the outbreak of the disease should take place within the same period of time even after trauma.

Apart from such cases where chronic polyarthritis commences with an acute attack, it begins in a relatively lingering form in some joint and gradually spreads to other joints. The claim that the time interval should be as short as possible cannot directly apply to this type of chronic polyarthritis, which is assumed to have a causal connection with trauma. The condition that no time interval should exist, which is free from symptoms, in the development of the disease: traumatic chronic polyarthritis of the joints, is one that must be insisted upon here, just as in the case of acute polyarthritis.

In the same way polyarthritis should commence in the injured

joint. This condition is also essential. In the case of acute polyarthritis arising within a short interval, we may perhaps venture to assume a causal connection with trauma, even if the polyarthritis does not start in the injured joint. In the case of chronic polyarthritis however, where the time interval is often relatively long, this condition cannot be set aside. If we venture to assume a connection between trauma and a disease which develops chronically and is localised in different places; and if at the same time we wish to support our claim by referring to certain clinical cases, we must insist that this chronic disease should begin in the member first injured.

As long as we cannot experimentally produce or cause chronic polyarthritis by means of trauma, and thereby also demonstrate that this polyarthritis commences in a joint which was not affected by the trauma, we have no right to dispense with this condition regarding localisation. When the condition, that polyarthritis should begin in the injured joint and that there should not be any time interval free from symptoms, concerns chronic polyarthritis, it also entails, in actual practice, that while the first symptoms still remain in the injured joint, arthritic alterations should develop in other joints frequently symmetrical ones.

The question is not only of great theoretical interest; but is, in one sense, of equal practical significance. At present, a patient suffering from primary chronic polyarthritis, which manifests itself in connection with trauma, is not generally considered to be the victim of an accident. Consequently, as a rule, compensation is refused in accordance with the laws regulating cases of accident. This circumstance clearly reflects the view prevalent in leading medical circles in our country. It is possible, that the examination of more ample data would cause the present attitude to be revised. In any case, the question certainly merits further investigation.

During 1940, at least ten clear cases of chronic polyarthritis following upon trauma were treated at Nynäs Sanatorium. The author has, on this account, gone through all the journals respecting patients who suffered from diseases of the joints and were treated at this sanatorium between 1933—1940. Cases of relapse have not been included; even though the anamnestic data seemed clearly to indicate that the relapse was due to trauma. Further-

more, all cases have been excluded where there was uncertainty regarding the reciprocal connection between trauma and the appearance of the symptoms in the joints.

After this process of elimination, the data contain nineteen cases of chronic polyarthritis where the connection between a former trauma and the outbreak of the disease seems probable. Of the seven cases at Nynäs Sanatorium which were published earlier by von Koch, three are here included. The collected data represent 2.1 % of the whole clientèle of the Sanatorium. This figure however, should be taken *cum grano salis*, since the anemnestic data were collected by different investigators over a period of some years. Particularly, as at an earlier stage no special attention was paid to the connection between trauma and polyarthritis.

From 1933—1935, one of these patients was admitted; between 1936—1938, 2—4 patients each year; in 1939 and 1940, 7 and 2 patients respectively. Of these nineteen cases, sixteen were men and three women. This ratio of sixteen to three is very different from the proportion of the sexes usually found in cases of chronic polyarthritis. In the data under examination the women are greatly in the minority; whereas, as a rule, among patients suffering from chronic polyarthritis, the number of women is from 60—70 %. (According to Kahlmeter and others).

The respective ages of the patients are given in Table I.

Table I.

Age	10—19	20—29	30—39	40—49 years
Men	3	3	3	7.
Women			3	

All the women are between 30—39 years of age. The men are more evenly divided in decades; except for the period 40—49 years which contains seven cases. Since nursing homes under the Ministry of Pensions do not admit patients above this age limit, there is no case over 50 years of age in our data. All the men were manual workers: Stonebreakers, mechanics, woodcutters, farm labourers, dish-washers and electricians. This is quite natural, since the risk of trauma is greater in these occupations than in others.

worked the stiffness off. At Christmas 1938, he found it difficult to dress and undress on account of stiffness in the shoulders. Pain in his wrists and knuckles made it hard for him to attend to his work. The patient continued to work, with short interruptions in spite of the fact that his pains increased every month. He consulted a doctor in March 1939; the red-cell sedimentation reaction was then 48 mm. He was susceptible to throat infections, and he had his tonsils removed in May 1939.

The patient was first admitted to Nynäs Sanatorium in June 1939. X ray: skeleton of the hand showed slight decalcification . . . slight destruction of the condyle of metatarsal V of both feet, but no other alteration. He was again admitted to Nynäs Sanatorium in 1940. He started to work six months after his first discharge; but the pains in his joints returned and were now principally in the knee and ankle joints.

In the spring of 1940 the red-cell sedimentation reaction was 40 and 38 mm. On admission it had been 45 mm.

In this case, the patient had received a blow to his right foot, which caused periodical suffering. During the first period this was limited to the injured foot. After 5—6 months (the actual time is uncertain) similar symptoms appeared in the left foot, and during the subsequent months spread further to other joints. The patient's tonsils were diseased and his teeth were bad.

*Case No. 3.* Journal No. 438/1933 and No. 430/1934. Born 1887. Farm foreman. In May 1933 trauma of left foot which gave rise to a fracture of the metatarsus. A fixation bandage was applied and the patient was confined to his bed for three weeks. When he was allowed to get up again the foot was still swollen and painful. In accordance with the doctor's advice he began to work again. After a couple of weeks his condition grew worse, and the patient was admitted to hospital. During his stay in hospital pains started in his right foot, and the pain worked its way up into the leg so that pain and rigidity affected the knee and the patient was unable to walk. When these complaints grew less, they were replaced by pains in the groin, hip and the lumbar-thoracic cervico-spine; there was also pain and restriction of movement in the right shoulder blade. The patient was afebrile. On returning home he was unable to work until November 1933, when he was admitted to Nynäs, and the red-cell sedimentation reaction was then 12 mm. Some of his teeth were slightly carious; no other bacteria foci were discovered. The patient had to be readmitted in the autumn of 1934. On both occasions his condition improved; but it was considered impossible for him to return to his former occupation.

At an earlier period, the patient had sustained two traumata: in 1917 he had been kicked in the forehead by a horse. This had later affected the hearing of his left ear. In 1930 there occurred a fracture of the right metatarsus. In six weeks this was completely cured.

Here we have a case of trauma to the left foot, causing a fracture of the metatarsus and two and a half months later developing into chronic polyarthritis.

*Case No. 4.* Journal No. 727/1935. Born 1896. Stonebreaker. In the summer of 1934 the patient met with an accident, injuring his right elbow. The joint swelled up and became stiff. This passed, but after some time the slight pain and stiffness that was felt on making movements began to increase. Some months later similar difficulties were experienced in connection with the left elbow. Neither elbow could be fully stretched out. Later, a slight sense of stiffness and pain were felt in the shoulder, wrist, ankle and knee joints and in the left hip on moving. Lassitude. No reduction in weight. Temperature was not taken. On admission to Nynäs Sanatorium in 1935 the red-cell sedimentation reaction was 20 mm; this subsequently fell to 2 mm. Slight alveolar pyorrhea. The tonsils were in good condition. The periarticular capsule of the elbow joints was swollen, there was a defect in ability to stretch of 30°, and pain was felt on moving; also restricted abduction of shoulder joints and rotation right=left. The patient was unable to clench his fists properly and his grip was impaired.

A case of trauma in one elbow, where the symptoms disappear fairly rapidly; but after some time reappear. In the course of a few months they spread to other joints. The elbows were the joints which were most affected during the whole illness.

*Case No. 5.* Journal No. 335/1936. Born 1916. Electrician. Several small traumata here and there. During his school years the patient had suffered from scrofula of the eyes. From time to time he had experienced nasal obstruction. Suffered from tonsilitis at the age of four, since when he had been seldom troubled by throat infections. In September 1934, trauma in right leg (knee). Within three days the knee had become swollen and painful. In 1934 he visited the hospital and plaster was applied for two periods of three weeks.

X ray: negative. Later on the swelling in the knee increased. In July 1935 a specimen excision was performed on the right knee — the result showed hyperplastic follicular synovitis. New plaster was applied. Some months later, the swelling and stiffness in the ankles and left wrist increased. The red-cell sedimentation reaction was under 80—50. The patient lost 16 kilos in weight.

On admission to Nynäs Sanatorium the red-cell sedimentation reaction was 71 mm. The patient's throat and teeth were in good condition. The tonsil cavity was empty. X ray of the skeleton of the knee and hand: the alterations were mainly localised in the knee and ankle joints.

A case of polyarthritis developing in connection with a protracted, obstinate, traumatic monoarthritis of the knee joints. No bacteria foci were observed.

*Case No. 6.* Journal No. 223/1937. Born 1918. Mechanic. At the end of August 1936 trauma of the left knee. The swelling and stiffness increased. The patient stopped working three days after the accident. Nearly simultaneously with this, the patient experienced sensitiveness in the left ankle and under the sole of the left foot when walking. He con-

*Case No. 8.* Journal No. 373/1939 Born 1911 Repairer. On September 22, 1938 a heavy piece of iron fell on his right foot. He limped, but tried to play football in spite of the injury. He put his foot in cold water to ease the pain. On October 5 the swelling and pain in the right foot increased. On October 7 the patient was admitted to a cottage hospital. He was subfebrile. The red-cell sedimentation reaction showed 38 mm. Shortly afterwards, swelling, stiffness and pain were experienced in the right knee, the left ankle and the toes. When he was discharged on December 18, the red-cell sedimentation reaction showed 20 mm. He was unable to work during the whole of the spring of 1939 on account of pains in the feet. He was admitted to Nynäs on March 31, 1939. During his stay the red-cell sedimentation reaction showed 13—47—21 mm.

The patient walked unsteadily, with legs wide apart. His feet were most affected. He had flaccid, cleft tonsils. The X ray taken on April 4, 1939 showed decalcification in the skeletons of both feet. The joints' space had everywhere retained its height. No destructions were observed. Local, spotlike attenuations were noted in the condyle of metatarsal I on both sides.

He was discharged as his condition had improved. The patient was able to work until the spring of 1940; when, as a result of an acute attack of gastro-enteritis, there was a recurrence and intensification of the process in the feet, hips and right knee. He was readmitted to Nynäs on August 21 1940. The red-cell sedimentation reaction showed 26—11 mm.

Slight swelling was observed around the fastening of the Achilles' tendon of the right foot; and there was slight tenderness on pressing, and the second toe of the left foot was somewhat swollen.

The patient was X rayed on June 25, 1940. The skeleton of the foot only manifested slight decalcification. On the underside of each calcaneus were spur-formations together with slight destruction. In addition to this, slight destruction was noticeable in the right metatarsal V. A former examination had shown a periostitis to be present on this metatarsal bone; this had now disappeared.

When the patient was discharged on September 11, he only felt slight pain in the right knee after exertion. He could stand on his toes; and except for crepitation, his right knee was in good condition.

Here is a case of trauma of one foot giving rise to arthritis, and in conjunction with this developing into general polyarthritis. In this case, beside the trauma, there was a significant factor — the local chill to the injured foot. Furthermore, the patient's tonsils were flaccid and cleft. These were removed at a later date.

*Case No. 9.* Journal No. 716/1938. Born 1923. Stonebreaker. On June 16, 1938 the patient received a blow from a sledgehammer to his left hand. The hand was swollen and mobility restricted. The patient experienced pain in his hand, and a feeling of weakness in his whole arm. He continued to work; but the symptoms grew so much worse that he had to stop. On August 4, he took medical advice. As it was suspected that this



might prove to be a case of tuberculosis, the patient was sent to hospital. At his juncture, pain began to be felt in the left ankle when moving.

An X ray of the left hand showed a condition of diffused atrophy. In all other respects conditions were normal; this also applied to the skeleton of the foot. During his stay in hospital the red-cell sedimentation reaction showed 29—21 mm.

At the commencement of his hospital term the patient complained of pain on moving his right wrist. When the patient had caught a cold, which was accompanied by rhinitis and infection of the throat, the symptoms which already existed in the joints of both hands and in the left foot were aggravated. After the patient's discharge from hospital and until he was admitted to Nynäs he had two periods of relapse, during which stiffness and pain on moving were felt in the left elbow.

On admission to Nynäs on June 26 1939 arthritic alterations were observed in the wrist and finger joints, and in the left elbow and the left ankle. On his discharge, the patient had almost completely recovered. In three months' time he started to work again. Three months later he felt a sense of stiffness and tenderness in the proximal finger joints, and in the joints of wrists, elbows and ankles.

The patient was readmitted to Nynäs Sanatorium on August 2, 1940. The red-cell sedimentation reaction during his stay at the sanatorium showed: 13—18—9—20. The results of the X ray taken, were the same as before. He had small tonsils free from any signs of irritation. The teeth were in good condition. The small finger joints, the wrist, elbow and ankle joints were all affected. On discharge his condition had improved.

Here we have a case of progressive chronic polyarthritis developing in connection with an injury to the patient's hand, without there being any bacteria foci observed. About two and a half months after the trauma had taken place, the first lingering symptoms were observed in the other joints.

*Case No. 10.* Journal No. 39/1940. Born 1901. Farm-owner. On November 5, 1937 patient sustained trauma to his left wrist with fracture of os hamtum sin. Plaster was applied. He continued to work; but felt pain in his wrists; and these were swollen. In April 1938, the right elbow began to get stiff and sensitive. The patient was treated for a month at the Cripples' Hospital. The red-cell sedimentation reaction showed 45—58 mm. His condition did not improve. He was then admitted to hospital and treated there from November 25 1938 to March 24 1939. Diagnosis: Polyarthritis chron. posttraumatica + pes. plan. bilat. + Caries dent. + Otit. med. chron. dext.

He was afebrile and the red-cell sedimentation reaction showed 62 mm. The left wrist, right elbow joints and the right foot were all affected. The patient's health improved. Later, his condition deteriorated, and he was admitted to Nynäs on January 9, 1940. The red-cell sedimentation reaction showed 25 mm.

The left wrist, the right elbow and the right shoulder joints were affect-

ed. The right knee was somewhat stiff; on moving, the right hip and the right ankle proved sensitive.

An X ray of the left wrist showed destructive arthritis; the right wrist was in good condition. Both left and right shoulders were in good condition. The right elbow was affected by arthritis. During his stay at the hospital his red-cell sedimentation reaction showed 25—7—20 mm.

On his discharge, symptoms continued to be observed in the left wrist and right elbow joints.

A case of a left-sided fracture of the wrist, which in spite of treatment did not become free from symptoms; but after about four months symptoms were also observed in other joints. Chronic bacteria foci were established.

*Case No. 11.* Journal No. 772/1939 and No. 203/1940. Born 1890. Blaster. In 1938 the patient dislocated his right knee, and went about, for fourteen days, with the knee swollen. He attended the surgical polyclinic: a plaster cast was applied first, and later, an elastic bandage. He never fully recovered. He went to work with a swollen and stiff knee. Five months later the patient had pains in the groins and experienced difficulty in walking; whereupon he again attended the surgical polyclinic. Plaster and an elastic bandage were applied; he also underwent a rest cure but without beneficial result. Consequently, a specimen excision was made. As at the same time pain and stiffness developed in the right shoulder the patient was removed to the medical department, where he was treated for five months during 1939.

General conditions: More and more of the large joints became affected. In this respect, the knees were the worst, and the right one was particularly swollen. The red-cell sedimentation reaction showed 138—114 mm. For the time being, the patient's condition was so much improved that he could walk alone.

On admission to Nynäs on July 14 1939, the patient suffered most from swelling and pains in the knees on moving; especially in the right one. Difficulty was experienced in walking. The red-cell sedimentation reaction showed 111 mm. The tonsils were somewhat flabby and smeary; but there was no sign of acute irritation. The teeth were bad. On July 17 1939, the knee joints were X rayed: Decalcification and sharpening of the limitation of the joints' surface was observed. Right tibial condyle showed attenuation size of a finger-tip, which continued as far as the joints, and was probably due to an old impression fracture. Hip joints: slight decalcification. Right shoulder: smallish osteophytic formations at limitations of the joints' surface — a sign of arthritis deformans. A grinding surface was also observed on the lower surface of the acromion, which indicated rupture of the supraspinatus. The left shoulder was in good condition.

The X ray on October 9 1939 of the hip joints showed slight decalcification. The patient's condition improved; but he was readmitted on March 15 1940 in order to continue his treatment. In the meantime he was able

to undertake light work until the cold weather set in. The large joints continued to be those primarily affected, especially the knees.

X ray showed that the hip was now in good condition. Knee joints: calcification improved; otherwise, the same condition as before. There was no change in the condition of the shoulder joints. The skeleton of the hand was in good condition.

The patient continued to go about for five months while suffering from traumatic arthritis of the knee; whereupon a lingering polyarthritis developed which affected most of the large joints. During the whole course of the illness the two knee joints were most affected and were also the most difficult to cure.

*Case No. 12.* Journal No. 1024/1939. Born 1896. Dishwasher. On May 21 1939 the patient slipped and dislocated his right foot. After some days it became so swollen that he could no longer walk. It was looked upon as an accident arising out of his work. In a week's time the other foot was also swollen. He was admitted to the surgical department. Within sixteen days the left knee and the left wrist were swollen, and the former was tapped. The patient was then transferred to the medical department. He was afebrile. The red-cell sedimentation reaction showed 37—10 mm. He had bad teeth, and these were now attended to. The patient's condition improved. He was admitted to Nynäs on September 13 1939. He had no teeth. The tonsils were cleft and of normal size. His gait was stiff and unsteady. The foot and toe joints were most affected. During his stay in hospital the red-cell sedimentation reaction showed 5—4 mm.

A case of polyarthritis manifesting itself in a subacute form in a good week after the trauma to the foot had occurred. Throughout, the foot-joints continued to be the least susceptible to treatment.

*Case No. 13.* Journal No. 1306/1938. Born 1911. Dairyman. In 1938 the patient's right hand was crushed. »A fracture of the tendons» was established. Plaster was applied. When this was removed, the hand was stiff and the patient was unable to use it. He received special treatment for fourteen days to make the joints pliable. The right hip and the left great toe were now swollen and painful. He was treated in hospital for two months. During this period the red-cell sedimentation reaction showed 56—32 mm. He was afebrile. While he was in hospital he had pains in the shoulders. When he was discharged his condition had considerably improved; but in two weeks' time he suffered a relapse. On admission to Nynäs on December 19 1938 the symptoms were now especially noticeable in the shoulders and in the acromio-clavicular and hip joints. Volar sensitiveness of the right wrist was experienced; but for the rest, it was in good condition. The red-cell sedimentation reaction showed 17—20 mm. The tonsils were in good condition. During the last few years he had had trouble with his teeth. Inflammation and destruction at the root of + 2 was observed. The patient also suffered from diabetes mellitus.

The patient's symptoms begin in a traumatized and plastered wrist, when this is mobilized two months after the trauma occurred.

*Case No. 14.* Journal No. 899/1939 and No. 633/1940. Born 1889. Confectioner. In June 1938 the patient's wrist had been sprained. It swelled up at once and became tender. It was better in a week; and the patient continued to work but with difficulty. At the beginning of July it was still swollen, and stiffness and sensitiveness were experienced in the right wrist. In two or three weeks, the patient's condition improved; but now there was stiffness in the right shoulder and its mobility was restricted. During August the symptoms in the right hand and right shoulder were less pronounced; while now the same symptoms began to be observed in the left shoulder. Some weeks later swelling, stiffness and sensitiveness were experienced in connection with the left wrist. During the autumn of 1938 the patient complained of lassitude, and sensitiveness in the legs. About July 1938 the ankles were swollen; while the feet became stiff and tender under the soles and in the arches.

Subsequently, different joints were affected; but the worst were the right wrist and the ankles. The patient received hospital treatment from March 9 to June 15 1939. He was admitted to Nynäs on August 15 1939. The wrists and ankles were affected. The mobility of the shoulders was somewhat restricted. The red-cell sedimentation reaction showed 39—52—36 mm. The patient's condition was greatly improved; and he began to work as soon as he was discharged. Very soon however, he suffered a relapse as regards the condition of his feet. After this he could only do light work. He continued to grow worse and was consequently readmitted to Nynäs on August 19 1940. During his stay the red-cell sedimentation reaction showed 53—98—118 mm. The feet and the right wrist were affected. X ray on August 23 1940 showed the foot skeleton to be slightly decalcified. Since the last examination slight destruction had taken place in the first joints of the IV toe. There was no change as regards the first joints of the III toe. Furthermore, cartilage reduction had taken place in every talo-navicular joint; but the tarsus was in good condition. The ankles were also in good condition. In the right hand: considerable arthritic destruction was observed in the wrist; this consisted in cartilage destruction and slight destructions. There were no alterations in the finger joints. The left hand and the lungs were in good condition. On the patient's discharge his condition generally remained about the same. A new cure was proposed.

A case of a medium but protracted chronic polyarthritis appearing in less than two months after a traumatic monoarthritis. During the whole period, the traumatic joint was among those most affected. No bacteria foci were established.

*Case No. 15.* Journal No. 302/1936. Born 1906. Chauffeur. On October 18 1935 the patient dislocated his left foot. He attended the surgical polyclinic. X ray gave a negative result. The patient was requested to return some days later, when a plaster cast was applied. A week after this, he commenced to feel pain in his wrists, and somewhat later these were swollen. On October 31, he had fever. The plaster cast was removed

and the patient was admitted to the medical department; here he was treated until November 10 1936. The red-cell sedimentation reaction showed 100—18. During his stay at the hospital the knees were also affected; especially the left one which was very swollen. It was tapped. The guinea-pig test gave a negative result. On discharge his condition had improved. While he remained at home his condition continued to improve.

On April 3 1936 he was admitted to Nynäs. Symptoms were observed in the knee and ankles. He was discharged as fully recovered. The red-cell sedimentation reaction showed 9—13—6 mm. The patient had formerly suffered from iritis; this was now considered to be fully cured. The tonsils were very hypertrophied and scarred. He had lost several teeth.

A week after the trauma to the left ankle had occurred, while the patient was walking about with a plaster cast, a lingering polyarthritis developed which first affected the wrists.

*Case No. 16.* Journal No. 305/1940. Born 1890. Smith. Generally speaking, he had always been healthy. Only in later life he had had trouble with his teeth. He now only had artificial teeth. In May 1939 he had received a blow to his left knee. Within fourteen days it had swollen up, and there was stiffness and sensitiveness. He continued to work until June 26, when he was admitted to hospital. He had a ganglion at the back of the left knee and an effusion. 80 cm<sup>3</sup> were removed on tapping the left knee. Extirpation of the ganglion. While he was confined to his bed, he suffered from embolism of the lungs. This necessitated him staying another seven weeks in bed. During this time he experienced pain and stiffness in the wrists, the knee, elbow and finger joints. In October 1939 the left knee was tapped again. The red-cell sedimentation reaction showed 24—33.

He was admitted to the medical department in February 1940 on account of his polyarthritis; and he was treated policlinically until he came to Nynäs on April 24 1940. X ray of the knee joints showed a moderately pronounced, diffuse decalcification. The contours of the joints were sharp. The right elbow and the knee joints were most affected especially the left one. The red-cell sedimentation reaction showed 41—19 mm during his stay. On discharge, his condition had improved; but he was unable to resume work. A new cure was proposed in six months' time.

Two months after the attack of traumatic monoarthritis, the first lingering symptoms of chronic polyarthritis were observed. During the whole course of the illness, the injured joint was among those most affected.

*Case No. 17.* Journal No. 77/1937. Born 1898. Married woman. In 1934 the patient «dislocated» her right knee, which became swollen. She had a little fever, and the wrists and finger joints were somewhat sensitive. In six months' time she had recovered. In January 1936 another «dislocation» of the right knee occurred; the knee was again swollen. She got up; and after a month she felt pain in her wrists and finger joints. The ankles were also painful and swollen. She walked with difficulty during

the whole of the spring of 1936. She first consulted a doctor on June 1. She was then subfebrile, and the knee was tapped. She was confined to her bed for four weeks. Her condition grew worse, and she was admitted to hospital from August to October.

On discharge, the patient felt some signs of stiffness in the heels; in all other respects she was quite all right. When she had left the hospital she had her teeth extracted; whereupon she again had fever, and the joints became more seriously affected. She was confined to bed for a week. Her condition improved gradually.

She was admitted to Nynäs on Januari 27 1937. The red-cell sedimentation reaction showed 5 mm. X ray of the right knee joint showed diffuse decalcification without arthritic deformations or any other alterations in the skeleton. The flection of the right knee was slightly arrested; the same applied to the dorsal flection of the right foot. Pain was felt in connection with the max. flection of the right knee. Possibly exudation in the interphalangeal joints dig II—III dextra. Several teeth were missing and the tonsils had been removed.

After the first trauma to the right knee there were slight symptoms of polyarthritis. In connection with the second trauma to the same knee, symptoms in other joints appeared within a month. There was a temporary recurrence of the complaint in connection with the extraction of the patient's teeth. Bacteria foci were located around the teeth, and had probably also existed at an earlier date in the tonsils.

*Case No. 18.* Journal No. 1067/1939. Born 1905. Married woman. In July 1938 the patient dislocated her right foot. Within three days the swelling and pain in the foot increased, and the patient had fever up to 39°. The infection spread rapidly to the wrists, finger, knee and toe joints. She was confined to her bed for three months, and was admitted to hospital, where she received treatment from October 1938 to January 1939. During the summer of 1939, her condition, which had been improving, deteriorated, and she was consequently admitted to Nynäs on October 10 1939. The red-cell sedimentation reaction showed 15—8 mm. She experienced »sensitiveness in the glands when it was cold.» On admission, it was principally her ankles that were affected.

A case of polyarthritis starting in an acute form after a trauma to the right ankle and then developing chronically. The tonsils were most likely a chronic source of infection.

*Case No. 19.* Journal No. 1229/1939 and No. 1074/1939, and No. 720/1940. Born 1899. Married woman. In July 1937 received a blow to the left knee, which swelled up. She went about during the whole of the spring of 1938 with a swollen knee. When she consulted a doctor tuberculosis was suspected. In June she was admitted to hospital for examination. The knee was tapped and x rayed: and the patient was allowed to return home. While she remained at home, the joints began gradually to be increasingly affected. The wrists, and the joints of the shoulders, hips, jaws, and left knee, and the neck were all affected. Swelling, pain and

stiffness were observed. She probably went about with a subebrile temperature; there was no infection of the throat, nor any other known cause to account for temperature. During the whole period the left knee was most affected.

She was admitted to Nynäs on November 30 1938. The red-cell sedimentation reaction showed 34 mm. Most of the large joints and the small joints of the hands were affected. On discharge, her condition had improved. Only in the left knee and the ankles were any larger alterations observed. She was admitted again in 1939 and 1940. Each time it was the left knee that was the most affected joint and was also least susceptible to treatment. The patient had a benignant goitre of moderate size.

A case of traumatic monoarthritis which in six months developed into a serious case of chronic polyarthritis. No chronic bacteria foci were observed.

### Trauma.

Before any significance can be attached to a trauma in connection with chronic polyarthritis, the former must be characterised by a certain size and gravity. In the case histories under review there are three instances of the trauma causing fractures. In four other cases a plaster cast was applied; and in five further cases tapping or some other operative measure was taken, in connection with the joints themselves or with parts of the body close to them. In two cases tubercular monoarthritis was suspected.

The traumata consisted in: a fall injuring the elbow; falling on a cement floor; falling down stone stairs; knee knocked against an iron beam; blows from a shovel and a sledge-hammer; a knock sustained when jumping; dislocation and crushing (sprain) of various joints and members.

### Local Symptoms and Their Diffusion.

Local symptoms have arisen in direct connection with the traumata and must be considered as being caused by these. The patient has suffered from pain and swelling in the injured member. Where a non-elastic bandage was not applied, movement caused tenderness and pain. In spite of therapeutic treatment exudation has recurred. Functions have been restricted; the patients limped; they were unable to bend or stretch fully. The symptoms have been periodically aggravated; especially when the patients tried to work. Symptoms have gradually appeared in other joints while they continued to be observed in the joint that was injured

first. In a few exceptional cases, where development was more rapid, the symptoms in the joint that was first injured, have decreased simultaneously with the appearance of arthritic alterations in other joints. This variation in the course of the disease is not at all unusual in cases of chronic polyarthritis. The development has, in all cases, been such as in customary in chronic polyarthritis. In many instances polyarthritis has first manifested itself as sub-chronic monoarthritis; but in other cases, the disease has, from the very outset, taken the form of an acute attack of polyarthritis.

### The Time Interval.

The time interval is shown in Table II. The cases have been arranged in accordance with the time that elapsed between the occurrence of the trauma and the appearance of the symptoms in joints other than the one first injured.

Table II.

<i>Time Interval</i>	<i>Men</i>	<i>Women</i>
Days 1—7.....	1	1
Weeks 1—4.....	3	
Months 1—6.....	12	2
Total	16	3

If we examine the case histories in detail we shall find that the time interval varies from three days to six months. The knee joints, ankles and wrists are usually the members which are primarily injured; and together they cover the whole range of the time interval. Thus the time interval for knee injuries varies from three days to six months; that for foot injuries from three days to five or six months, and the interval for hand injuries extends from five or six weeks to four months. On an average, the time interval is longer for knee injuries and shortest for foot injuries.

### Conclusion.

The cases are found to comply with the conditions, which were stated at the commencement of this article, to be requisite, if we are legitimately to postulate a causal connection between a trauma and the chronic polyarthritis that subsequently develops.



## Analysis of the Case Histories.

We find that in seven cases the primary injury was to the knee joint, in six to the ankles and in five to the wrists; finally, in one instance it was the right elbow joint that was first injured. As might be expected, it is the knee, ankle and wrist joints that dominate. These joints are the most susceptible to trauma and are often attacked by chronic polyarthritis.

It is noteworthy that our data does not furnish us with a single case of a traumatic shoulder joint developing into polyarthritis. Trauma frequently occurs in connection with the shoulder joint, which plays a very prominent functional part and is very extensively subject to polyarthritis among middle-aged and elderly patients. Consequently, we might have expected to find the shoulder joint represented among the injured joints as often as the knee, ankle and wrist joints.

As it may prove of interest to note the condition of the injured joint during the period extending from the occurrence of the trauma to the appearance of the symptoms in other joints, particulars will be found in Table III. The Table also furnishes information concerning the duration of the time interval and the nature of the bacteria loci. The latter problem will be dealt with more fully at a later stage.

A cross in parentheses: (+), indicates that the anamnestic data show that the patient had suffered from an infectious disease, which may have contributed in producing bacteria loci.

We see that in five cases the patients did not freely use the injured joint, since either a plaster splint was applied, or the patient was confined to bed. The five injured joints consisted in: two knee and two ankle joints and one wrist joint. In fourteen cases the patient had overstrained the joint by continuing to work in spite of the fact that the symptoms were still observed. Some of the patients only ceased working when the symptoms actually prevented them from continuing. Others again, had the joints in question immobilised, either by the application of plaster casts or of supporting bandages for one or two months.

When these were removed and the patient had worked for some time, lingering symptoms were also observed in joints other than the injured ones.

Table III.

Case No:	Time Interval	Bacteria Foci	Functional Strain
18	3 days	+ (+)	— Patient confined to bed
12	2 weeks	+	— certified ill
8	2 weeks	+ (+)	+ played football and put foot in ice-cold water.
2	5—6 weeks	+	+ Worked most of the time.
3	2 ½ months	+	+ Supporting bandage. Rested 2 months. Worked a couple of weeks then symptoms appeared.
15	1 week	+ (+)	+ Walked about freely a few days, then plaster cast applied. Supported himself on wrists, which were then affected by polyarthritis.
6	3 days	+	+ worked.
19	6 months	— (+)	+ Worked.
16	2 months	+	+ Worked a months, then remained a month in bed.
5	4 months	— (+)	— At first walked about with non-elastic bandage, later 2 plaster casts applied consecutively. Received hospital treatment.
17	1 month	+ (+)	+ Attended household duties.
11	5 months	+ (+)	+ Worked 14 days, then plaster cast applied 6 weeks, followed by elastic bandage. After this worked.
7	6 weeks	+	— Worked 1 week, then received hospital treatment 1 month, subsequently certified ill.
13	2 months	+ (+)	+ Worked 3 weeks in spite of fracture of tendons; plaster cast applied 3 weeks, then received treatment to make joints flexible.
14	2 months	—	+ Worked.
1	5—6 weeks	+	— Plaster splint.
10	4 months	+	+ Plaster cast about a month, then worked.
9	2 ½ months	—	+ Worked 2 months, then received hospital treatment.
4	2 months	+	+ Worked
		Total + 15	+ 14
		— 4	— 5

In the case of the patient who played football in spite of the injury to his foot, polyarthritis manifested itself in an acute form and spread rapidly to other joints. In addition to this, the patient had put his foot in ice-cold water to ease the pain. In another case, symptoms began to be observed in other joints, while the injured joint was receiving treatment to make it more flexible. The injured joint had also been immobilised for a time.

The wrists of one of the patients had been secondarily affected, after he was up and walking by the aid of a plaster cast and crutches — he had overstrained his wrists in this manner.

It is a general clinical experience that various forms of infection can either promote or even cause an attack of chronic polyarthritis. Furthermore, it can be stated without hesitation that bacteria foci, which perhaps are in themselves insignificant, can help to maintain and even aggravate chronic polyarthritis, and that their removal can bring about a turn for the better. To what extent this applies to our data will be examined presently.

If we return to the anamnestic data, we shall see that one of the patients (Case No. 13) suffered from diabetes, and Wassermann's reaction gave a positive result. Both these facts had been established three years prior to the trauma. He had also formerly suffered from acute otitis and gonorrheal urethritis. The latter complaint had been treated, and was stated to have been cured six years ago. Three other patients had suffered from urethritis gonorrhoeica, but in all three cases the infection had been contracted many years previously — in fact, fifteen years or more. Cases No. 8 and No. 11, had both had abscessus peritonsillaris three years previously; and No. 8 had subsequently suffered from lymphadenitis, which had been extirpated a year before the trauma occurred. Case No. 11 while waiting to be admitted to the sanatorium suffered from a reactive psychosis, which however, disappeared very quickly. In case No. 19, the patient had three years previously suffered from albuminuria, for a short time, which occurred in connection with angina. Case No. 15 had had iritis twice — the second attack took place a year before the trauma occurred. Case No. 17 had been troubled by cystitis. Finally, case No. 18 had suffered from peritonitis consequent on an attack of appendicitis eleven years previously. She had also had sinovitis six years ago. The patient had also had two serious abortions in the second and third months,

respectively five and four years previously. In Table III, (+) has been placed against this patient in the bacteria foci column. None of the patients had had in connection with the outbreak of the traumatic polyarthritis, any acute infection such as angina, pharyngitis-bronchitis, intestinal infections or infections of the urinary ducts.

The patients are always carefully examined in this respect, and no doubtful case has been included. On the other hand, it appears from a survey of Table III, that no less than fifteen patients on their first admission to the hospital or sanatorium had had bacteria foci somewhere in their system.

For instance, all the eight patients who had a relatively short time interval — from a few days up to six weeks — had had bacteria foci, such as bad teeth, root-stumps, inflammation and destruction, alveolar pyorrhea, chronic tonsillitis, adenitis or diseases of the gall ducts. Of the eleven remaining cases, where the time interval was longer, four were quite free from any bacteria foci, and in seven, these were located in the teeth or tonsils. The four patients who were free from any known bacteria foci, were three men and one woman. The oldest was forty-eight, and the youngest fifteen. None of them had been treated in hospital for the injured joint before the polyarthritis manifested itself. One patient however, had been under observation in hospital for some days. There is no reason at all to suppose that those patients who were without any bacteria foci, contracted their rheumatic infection during their stay in hospital.

If we glance at the cases where bacteria foci were observed, to ascertain the proportion of such cases in terms of the primarily injured joints we shall find that all six of the cases with injured ankles had bacteria foci. Of the seven cases with knee injuries, there were five where bacteria foci were observed; and of the five cases with wrist injuries there were three.

The number of the patients who had had bacteria foci and who had suffered functional strain was about the same: fifteen and fourteen respectively out of nineteen. Eleven patients had had both; whereas only a single patient had been free from bacteria foci and functional strain.

## A Suggested Method of Interpretation.

Since so many cases of chronic polyarthritis were found to have a connection with trauma, the necessity for an explanation became the more urgent. As the conception of the etiology of chronic polyarthritis changed, so the explanation of the part played by trauma also changed. It is only natural that when an attempt is made to interpret the role played by trauma that this will in turn depend upon our conception of the etiology of chronic polyarthritis. Even during the heyday of bacteriology, when specific bacteria were being searched for, in order to account for nearly every kind of disease including chronic polyarthritis, the opinion was expressed that trauma created a local disposition. It was held that the agents of infection that were the cause of polyarthritis could not develop in the blood-vessels, but were to be found in the edemata and hemotomata which appear after trauma. As no actual agent of infection was known that caused chronic polyarthritis, comparisons were made with gonohorreal polyarthritis and other diseases. Here the bacteria that caused the disease were known, and they could be demonstrated in the exudation. It could be shown that gonococci assemble in a joint that has either been injured by some blunt force such as a blow etc. (Jeaneret, Bergalone), or has been exposed to some operative measure (Mouchet et Bruvas).

The role played by trauma in creating a *locus minoris resistentia* was generally accepted. The change that has occurred in the conception of rheumatic diseases due to the investigations of Klinge, Rössle and Talajeff has also contributed in creating a new idea of the part played by trauma in the genesis of rheumatic diseases. Even if chronic polyarthritis is an infectious disease, it is the organism's allergic reactions that give the disease its characteristic features. The organism must be sensitized, and when under the influence of a stimulus it must react hyperergically.

Klinge believes that he has shown by pathologico-anatomical means that the diffusion of alterations of a rheumatic-inflammatory nature in an organ, depends on the functional-mechanical strain. This strain, which is able to influence the localisation of the rheumatic inflammation can be looked upon as a physiological trauma. An exterior strain could have the same effect. A trauma should be considered as the equivalent of an intensified mechanical strain.

Both can play a part in allergic functions, localise the process in a definite part of the body and cause the rheumatic infection to manifest itself. It has proved possible experimentally to sensitize an animal by means of albumen, and then to produce arthritis by subjecting the sensitized joint to a blow.

The conception of a *locus minoris resistentia*, as well as the significance of trauma as the localisation and manifestation of an allergic reaction, assumes a predisposed organism, by means of which trauma may produce chronic polyarthritis. One conception, sees the decisive factor in the existence of infection; whereas the other, is mainly concerned with an allergically reactive organism, which however, does not necessarily exclude the existence of an infection.

Klinge considers that chronic polyarthritis is an infectious disease. von Koch also bases his attempt to find an explanation on the allergic theory; but instead of the antigen having an infectious origin, he looks for an antigen of a different character. He points out that traumatic tissue is able to produce out of the organism's actual substances — by means of degeneration and autolysis — foreign matter that possesses the quality of an antigen. This matter can, if resorbed in bulk, sensitize the organism and produce allergic reactions.

In connection with von Koch's lecture a discussion was arranged, during which Kahlmeter stated that in accordance with the general view held by a large number of rheumatologists, we must assume that a latent, hyperergic condition exists prior to the occurrence of the trauma. This condition could be produced just as readily by an antigen of an infectious nature as by one of another variety. Westergren however, stressed the infectious nature of the allergen.

In my own data, fifteen of the nineteen patients had some form of bacteria foci on admission to hospital. These bacteria foci were in a clinically latent condition; but they had been observed when recording the status praesens of some of the patients on their admission to a hospital or sanatorium.

If we turn to the anamnestic data to look for any facts that might indicate the possible existence of bacteria foci, we shall find two cases where this is so, although the status praesens does not give any hint of this. One of the patients often suffered from nasal

obstruction and polyps, although on admission there was no evidence of this in the status praesens.

One of the women patients had suffered from angina three years before the occurrence of the trauma. As a consequence of the angina she had had albuminuria. Except for the angina, she was not susceptible to throat infections. The peritonsillar angina may have prepared the way for a chronic infection. But this however, cannot amount to more than a surmise. If we reckon with the possible existence of bacteria foci in these two patients, there only remain two patients where no infection was known, and where no indication of such a possibility existed.

If we accept Klinge's allergic theory, we are compelled, in the case of these two patients, either to assume that the antigen is not of an infectious nature, or that in spite of our lack of knowledge, a chronic infection is nevertheless present in their case. Personally, I should consider the latter alternative the more probable. Functional strain plays a great part according to Klinge's investigations in localisation of rheumatic inflammation. Therefore, not only ought the trauma of the joint and its environment prove of the greatest significance, but also the treatment of the joint after the trauma.

Table III, shows that fourteen of the patients had strained their injured joint after the trauma. According to the same Table, twelve patients had actual or suspected bacteria foci in their organisms. The two patients mentioned above, where neither the anamnestic data nor the status praesens showed any evidence in support of bacteria foci, had continued to work in spite of obstinate and progressive local symptoms. Here then is a clear case of functional strain. Four of the five patients who had not undergone functional strain, (since either plaster casts or splints had been applied, or the patient had been confined to his bed) had according to the status praesens bacteria foci. The anamnestic data indicated that even in the case of the fifth patient the existence of bacteria foci might be suspected.

Of the nineteen patients, twelve had been subject both to functional strain and to bacteria foci. In not a single case can both infection and strain be excluded.

It is remarkable however, how seldom trauma is connected with the appearance of chronic polyarthritis. In the data under

review from 1933—1940, only about 2 % of the cases of chronic arthritis could be attributed to trauma.

Traumatic injuries are in our time a common occurrence, and chronic bacteria foci are found very often, especially among poorer people.

Naturally, many do apply for professional treatment in the case of more serious traumata. The law regulating accidents incurred while at work tends in this direction. Consequently, many look after their traumatic joints; but there are nevertheless still a large number who endeavour to cure themselves, and do not rest the injured joint. Hence, we can assert that there are many persons who go about with chronic bacteria foci and meet with an accident causing trauma and then strain the injured joint without contracting polyarthritis.

Among the few where trauma is followed by chronic polyarthritis, many of these have suffered from a trauma before — in some cases this has happened several times — without any evil consequences ensuing. Consequently there must exist, among a small number of people, a factor of decisive importance for the development of chronic polyarthritis. It would appear that in some persons this factor varies in its capacity to become operative.

This factor may be taken to be the same as that common factor, which according to Klinge, makes the rheumatic diseases a single group. Primarily, this is the capacity of the mesenchymal tissue to react hyperergically and to develop specific inflammation foci. In the majority of our cases the existence of chronic bacteria foci has been proved. In a few of these cases the effect of the trauma has not been supported by functional strain. For these, as well as for such cases where strain alone was observed in connection with a trauma and there was no infection, a more intense hyperergic condition of the organism at the time the trauma occurred must be assumed.

We may suppose that only a weak hyperergic condition existed in such cases, where the earlier occurrence of a trauma was unable to cause polyarthritis, though a later trauma succeeded in doing so.

To sum up, I should like to say that a trauma affects a person who is in a condition »susceptible to rheumatic reaction» (Kahlmeter). The extent of this rheumatic condition differs from one pe-



son to another, and is even variable in the same person at different times. The trauma must occur when the person is in an optimum condition for the manifestation of the rheumatic infection.

### Summary.

The data comprise 19 cases of poly-arthritis -- 16 men and 3 women -- where an actual trauma to some large joint leads to a chronic disease of the joints. The proportion between the sexes is worthy of notice. These cases fulfilled the initial conditions that poly-arthritis should commence in the traumatized joint and that there must not be any interval free from symptoms. It is held that a causal connection between trauma and chronic polyarthritis has been established.

Primarily, knee, ankle, wrist and elbow joints were injured. These joints that were primarily injured continued to exhibit symptoms of arthritis, when the latter were already manifested in the other joints.

The time interval between the occurrence of the trauma and the secondary affection of some joint varied from 3 days to 6 months. The cases are equally distributed, as regards the length of the time interval, between these two points.

It is not possible, from the length of the time interval, to draw any strict line of demarcation between the cases caused by trauma and those that are not.

In 14 cases, the patients have at various times functionally strained the joint that was primarily affected. At the time that the trauma took place or poly-arthritis made its appearance, no acute infection was present. On the other hand, in 15 cases, chronic bacteria foci were known to exist.

Only one patient was actually free from both functional strain and bacteria foci.

In attempting to interpret the data, the author would point to the fact that bacteria foci and the mechanical strain of the injured joint are usually present. These two factors in conjunction with trauma are a common occurrence; whereas, chronic poly-arthritis due to trauma is a great exception. Consequently, these factors alone, cannot be deemed sufficient to explain the connec-

tion. The author assumes that the decisive part is played by the capacity of the mesenchymal tissue to react hyperergically.

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(From the Rheumatic Clinic of the University Hospital in Lund, Sweden).

## **Studies of the oxygen unsaturation in the venous blood of a group of patients with rheumatic disease in room temperature of 20° C. and 32° C.**

By

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### **Introduction.**

The law of the conservation of energy has recently passed its first centenary. Strangely enough, however, the expounder of this law, perhaps the most profound and universal physical law in our cosmic picture, is comparatively unknown. His name was Robert Mayer. Still less known, probably, is the fact that he was not a physicist but a physician, and that one of the observations which led up to his brilliant idea was a medical one.

When, as a ship's doctor of 26 years of age, he phlebotomized his sailors in the roads off Surabaja, he observed that the blood he drew was a brighter red than he was accustomed to from colder regions. On purely theoretical grounds he inferred that this must be due to the venous blood being more saturated with oxygen in these tropical regions, but he never succeeded in proving this, and it has for long been doubted.

According to Liljestrand the oxygen content of the arterial blood can be put at 17—20 volumes per cent. and its percentage oxygen saturation at 94—97. Arduous work and certain pathological states may cause slight variations in these figures, but on the whole they are relatively constant, unless anemia and reduced hemoglobin are present. The oxygen content of the venous blood,

on the other hand, varies very much in different organs of the body and under different conditions, work or rest being the factors that influence it most. Especially blood from the easily accessible superficial cutaneous veins shows great variations, which in all probability is associated with the fact that the blood flow in the skin not only subserves the local requirements of metabolism but also stands in the service of the regulation of heat. As early as 1925 Goldschmidt and Light showed that blood drawn from a surface vein on the back of a hand that had been kept in water at  $45^{\circ}$ — $47^{\circ}$  C. for ten minutes closely approximates arterial blood in respect of both oxygen content and carbon dioxide content.

With this fact in mind it is a ready assumption that under hot conditions, such as in the tropics, the oxygen content of the venous blood will be high and approach that of the arterial blood, as Mayer assumed so far back as 100 years ago. On account of unfavourable circumstances, however, this has hitherto not admitted of being demonstrated. Experiments have been made in hot-air chambers, but the ensuing perspiration and suchlike have vitiated the results, while experiments conducted in the tropics have evidently been lacking in sufficiently high-class laboratory facilities. Borchardt and Sundstroem also report failure in that respect.

Thanks to the technical skill and financial generosity of the Svenska Fläktfabriken one of the sick-wards in the Rheumatic Clinic of Lund was reconstructed in September, 1941, into a climatological laboratory. The arrangements enabled the climatic factors to be conditioned to a certain extent on tropical lines, that is to say, to be stabilized and adjusted to the desired temperature and air humidity. After the climatic conditions of this room had been stabilized and regulated to a so-called artificially dry tropical climate of  $32^{\circ}$  C. and about 35 per cent. relative humidity, with a range of variation amounting to  $1^{\circ}$  for temperature and about 10 per cent. for humidity, one of the first observations made was that the patients treated in it exhibited, on venipuncture, the bright-red venous blood observed by Mayer and others in the tropics. It could soon be ascertained that this colour was not primarily due to anemia. There remained Mayer's theory to test.

To this end we employed van Slyke and Neill's manometric method for determining the oxygen content of the blood. By this method the oxygen tension in the blood can be determined with an

error percentage of about 0.2 vol. per cent. per 1 cm<sup>3</sup> of blood. The blood was regularly drawn from the V. mediana cubiti early in the morning immediately after the patients had awakened and while they were still at complete rest. Venous stasis was avoided, and the blood was drawn in the customary manner under paraffin.

In order to have material for comparison other rheumatic patients than those treated in the climatological laboratory were also studied, as also were a couple of patients before, during, and after a stay in the artificial tropical climate.

#### *Observations on Patients.*

The patients T. B. and S. S. were two boys, aged respectively 14 and 16 years, with rheumatic fever in the active stage, while the rest of the patients were women, from 18 to 55 years of age, with rheumatoid arthritis in an active infectious stage. There was a considerable secondary anemia in a number of cases, a fact that is also evident from the tables. For instance, Case S. S., in which the haemoglobin value according to Zeiss was at first about 60 per cent. and afterwards slowly rose to 80 per cent.; at the time he was transferred to the so-called tropical ward this patient also presented an extremely malignant picture with Erythema annulare, symptoms of peritonitis, encephalitis and nephritis, transitory lung infiltration, etc. The patient I. K. also showed a secondary anemia of 68—70 per cent. according to Zeiss, and the majority of the other patients likewise had mild degrees of secondary anemia.

No circulatory disturbance of a central nature was present in any of these patients, nor any defect of the mitral valve, but in both the rheumatic fever cases the E. C. G. showed signs of a slightly affected myocardium, though not of any rhythmic disturbance. On the other hand, all the patients had a sensation of cold hands and feet, and especially the fingers of most of those with rheumatic arthritis were a pale, livid hue.

In an earlier work (Acta Med. Scand. 83.523) it has been shown that patients suffering from rheumatoid arthritis have to a great extent cold hands and feet, with a low skin temperature, which is doubtless associated with a constricted peripheral circulation in these patients, an assumption that is supported by several of the clinical symptoms presented by these cases (Acta Med. Scand. 103.90).

If the mean of the difference (oxygen unsaturation) for the rheumatic patients kept in common room temperature, viz. 8.22 vol. %  $\pm$  1.11, with a maximum of 10.94 vol. % and a minimum of 5.98 vol. %, measured by 20 determinations on 12 patients, is compared with the values obtained from a normal material, such as Lundsgaard's in which the corresponding figures for 38 determinations on 12 individuals were respectively 3.8, 8.95 and 2.70 vol. %, it will be found that the values obtained here are relatively

The first results obtained are indicated in the following tables.

Table 1.

*Oxygen content of blood drawn from V. mediana cubiti of resting patients with rheumatic infection and kept in common room temperature (20°)*

All samples drawn according to van Slyke's method (under paraffin) at 8 a. m. and in the form of duplicate samples, the mean of which has been taken.

Where the difference between the two samples is more than 1 volume unit, a note to this effect is made in the column «Remarks».

Date	Patient	Vol. % oxygen by van Slyke's method		Difference	Remarks
		in blood under paraffin	in blood after saturation		
18.1	H. H. ♀ 49 yrs	9.63	17.30	7.67	2 units diff. in paraffin bl.
5.2	H. H. ♀ 49 "	10.94	20.18	9.24	
9.12	B. J. ♀ 44 "	9.26	16.28	7.02	
11.12	H. B. ♀ 42 "	7.79	17.13	9.34	
14.12	H. P. ♀ 42 "	6.07	17.01	10.94	
11.1	I. B. ♀ 18 "	10.65	18.19	7.54	
12.1	I. B. ♀ 18 "	10.95	18.19	7.24	
25.1	E. P. L. ♀ 22 "	11.18	17.63	6.45	
29.1	S. M. ♀ 34 "	7.30	15.57	8.27	as well as in the saturated
1.2	K. B. ♀ 55 "	12.38	18.36	5.98	
3.2	E. B. P. ♀ 19 "	9.68	16.88	7.20	
8.2	E. L. ♀ 43 "	9.74	16.38	6.64	
17.2	H. P. ♀ 42 "	9.74	17.13	7.39	
22.2	H. B. ♀ 42 "	9.11	17.25	8.14	
19.2	I. B. ♀ 18 "	7.17	17.46	10.29	
15.2	T. B. ♂ 14 "	8.78	17.78	9.00	2 units diff. in paraffin bl.
12.2	S. S. ♂ 16 "	3.63	11.77	8.14	2 units diff. in paraffin bl.
24.2	I. B. ♀ 18 "	6.02	16.16	10.14	
29.3	I. B. ♀ 18 "	7.24	16.89	9.65	
7.4	I. K. ♀ 31 "	5.78	13.96	8.18	
Mean with stand. dev.		8.65 ± 1.82	16.88	8.23 ± 1.11	
Oxygen saturation		51.3 vol. %			
		± 10.73 vol. %			

Table 2.

*Oxygen content of blood drawn from V. mediana cubiti of resting patients with rheumatic infection and treated in so-called »tropical ward» (32° C.):*

All samples drawn according to van Slyke's method at 8 a. m. and in the form of duplicate samples, the mean of which has been taken.

Where the difference on apparatus readings between the two samples is more than 1 volume unit, a note to this effect is made in the column »Remarks».

Date	Patients	Vol. % oxygen by van Slyke's method		Difference	Remarks
		in blood under paraffin	in blood after saturation		
2.12	R. J. ♀ 22 yrs	15.89	17.75	1.86	
2.12	R. J.	15.89	17.75	1.86	
4.12	H. H. ♀ 40 yrs	11.47	15.54	4.07	
7.12	H. H.	12.21	14.80	2.59	
16.12	H. B. ♀ 42 yrs	12.24	16.47	4.23	Diff. in paraffin bl. 2 units
17.12	H. B.	12.24	16.03	3.79	
22.12	H. B.	13.81	16.03	2.22	
23.12	H. B.	14.05	16.03	1.98	
2.1	H. B.	13.25	16.03	2.78	
8.1	H. B.	12.97	16.49	3.52	Diff. in saturated bl. 3 units
20.1	H. B.	13.17	16.08	2.91	
10.2	H. B.	12.97	16.16	3.19	
13.1	I. B. ♀ 18 yrs	13.29	17.21	3.92	
15.1	I. B.	15.25	18.02	2.77	Diff. in paraffin bl. 2 units
22.1	I. B.	14.29	18.67	4.38	
12.2	I. B.	14.29	17.46	3.17	
19.2	T. B. ♂ 14 yrs	14.67	16.73	2.06	
26.2	T. B.	14.19	16.97	2.78	
19.2	S. S. ♂ 16 yrs	7.91	11.41	3.50	Diff. in paraffin bl. 3 units
23.2	S. S.	9.20	11.77	2.57	
26.2	S. S.	9.69	11.54	1.85	
22.3	S. S.	11.63	14.45	2.82	
26.3	S. S.	12.12	14.94	2.82	
1.4	S. S.	12.12	14.69	2.57	
Mean withstand. dev. 12.87 ± 1.49 15.79 2.92 ± 0.62					
Oxygen saturation 81.5 vol. %					
± 9.44 vol. %					

high. No doubt, however, this is in full agreement with the other above-mentioned clinical symptoms in these cases of a constricted peripheral circulation.

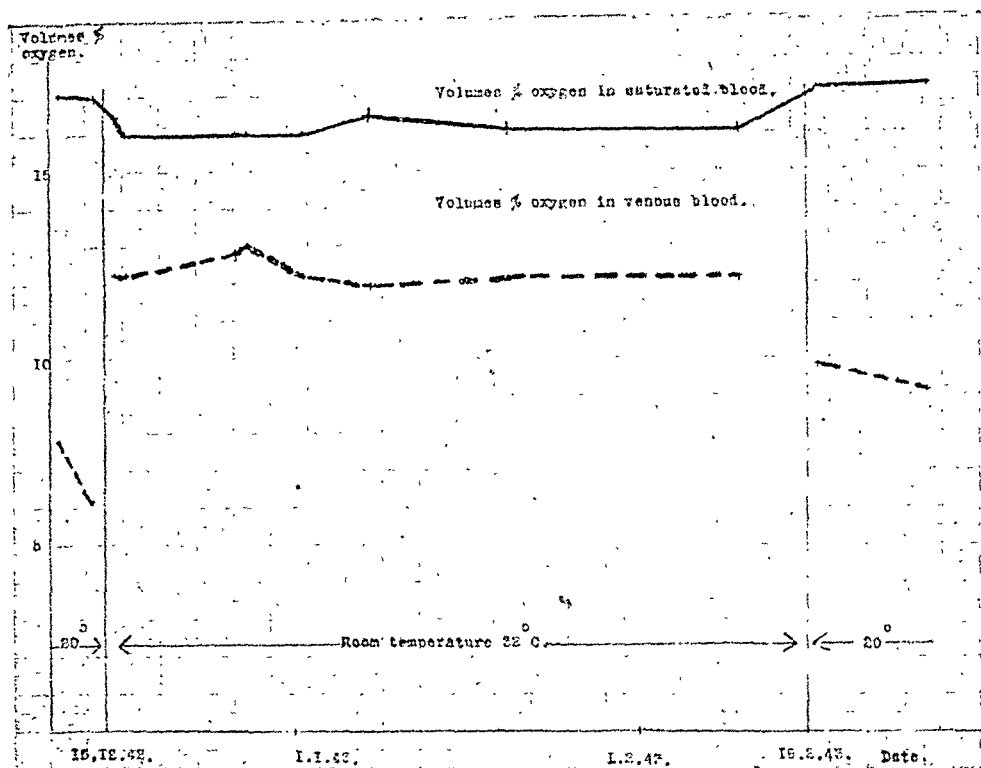


Fig. 1.

If, fig. 1, such a patient, e. g. Case H. B., is transferred from a ward having a common room temperature of  $20^{\circ}\text{C}$ . to the climatological laboratory with a temperature of  $32^{\circ}\text{C}$ ., it is seen that immediately after the transference the oxygen saturation is raised from a previous figure of 36 per cent. — a very low value for a patient at rest, but this patient also had markedly livid, cold hands and feet — to 74 per cent., the next day to 76 per cent., and a few days later to 86 and 88 per cent., in order subsequently to oscillate around 80 per cent. during the entire stay in the «tropical ward» and to descend again, immediately after return to common room temperature, to 57 and 53 per cent. An interesting point was that these last oxygen saturation figures were better than those recorded before the transference and accordingly constituted a parallel find to the observation that after removal from the «tropical ward» the patient had improved clinically and no longer had so markedly cold, livid hands and feet. The diagram submitted below records the oxygen saturation of this patient as well as the saturated oxygen content of her venous blood.

If the mean of the differences for the patients kept in a room temperature of  $32^{\circ}\text{C}$ . — 24 determinations on 6 patients —, viz.  $2.92\text{ vol. \%} \pm 0.62$ , with the highest value of 4.38 vol. % and the lowest of 1.85 vol. %, is then compared with the oxygen unsaturation in normal cases, it will be found that it lies immediately below the point usually set as the lowest



limit for such normal cases, 3 vol. %. Lundsgaard's lowest value was 2.70 vol. %.

The difference between these two mean values for rheumatic patients kept in a common room temperature of 20° C. and in 32° C. respectively is so large that it is statistically certain if errors of method can be left out of account. As already pointed out, however, there is an error percentage attaching to the method used here of about 0.2 vol. %, and therefore absolute certainty cannot be said to exist. However, the difference is so large that it may be statistically regarded as highly probable — the lowest value for oxygen unsaturation under 20° C. is here 5.98 vol. % and the highest under 32° C is 4.38 vol. %.

### Discussion.

It is evident from the investigation that under a common room temperature of 20° C. these rheumatic patients possess a relatively low oxygen saturation in the venous blood, measured in the V. cubiti in the morning on fasting patients at rest, viz. on an average 51.3 per cent. By way of comparison it may be mentioned that in normal individuals Lundsgaard found an oxygen saturation of 68 per cent. under the same conditions and that several other authors have found values that have also lain around 70 per cent (see Liljestrand). This relatively low oxygen saturation in the venous blood of superficial cutaneous veins under resting conditions can no doubt be put in association with the constricted peripheral circulation that also according to other clinical finds may be considered to be present in these rheumatic patients. Whether the trouble in that case lies in a constriction of the arteriovenous anastomoses, or in a capillary spasm, is difficult to decide. Probably both are contributive factors. The fact that a capillary spasm is concerned is directly discernible by studying, for instance, the number of capillaries in the nail-bed of these patients (see Edström), but this does not rule out the fact that here, as in normal individuals, the arteriovenous anastomoses may play a large part in the regulation of the blood flow through the skin and the subcutaneous tissues, primarily in the service of the heat regulation of the body (Havlicek, Vanggaard).

When patients of the same rheumatic type are kept in a room temperature of 32° C., however, the oxygen saturation in these cutaneous veins becomes higher. A mean value of 81.5 per cent. could be found here. Goldschmidt and Light had observed that by keeping the forearm in hot water at a temperature of about 45° C. a

relative oxygen saturation could be established in the venous blood, measured in the same way in the V. cubiti, of up to 92 per cent., i. e. a value bordering on that of the arterial blood. By keeping the forearm in water at a temperature between 29° and 39° C. these authors were not able to obtain a higher oxygen saturation in these veins than 69 per cent., and by keeping it in air at 26°—32° C. 75 per cent. Here, too, it is a question of a stay in 32° C. warm air, but the difference lies in the length of the stay and the constancy of the temperature. The effect seems to be considerably stronger here, since, in spite of the relatively low initial oxygen saturation, a relatively higher oxygen saturation is on an average obtained under the increased external temperature.

In these instances the tropical conditions are imitated as closely as possible, at any rate as regards a certain type of dry tropical climate. It ought therefore to be justifiable to speak of an artificial tropical climate and to consider the results as representative of the effects of the tropical climate. This applies especially to the conditions studied here.

Here, too, the observation has been made that, as in the tropics, the venous blood in, e. g., the V. mediana cubiti becomes bright-red under a temperature of 32° C. in the environs of the body, and it has been made clear that this colour is due to this blood being saturated with oxygen to a relatively high degree and approximating a degree of oxygen saturation that is typical of the arterial blood. It would therefore seem justifiable to assert that *this investigation confirms Mayer's assumption that the blood he drew from the V. cubiti on phlebotomizing his sailors in the tropics was bright-red on account of an oxygen content that approached that of the arterial blood.*

### Summary.

1. A report is made of a series of determinations by van Slyke and Neill's method of the oxygen in the blood drawn from the V. mediana cubiti in resting patients with rheumatic disease in common room temperature of 20° C. and in a temperature of 32° C.

2. In common room temperature of 20° C. the oxygen unsaturation of the venous blood was, on an average of 12 patients in 20 determinations, 8.22 vol. per cent.  $\pm$  1.11 with a maximum of 10.94

and a minimum of 5.98, or *51.3 per cent. mean oxygen saturation.*

3. *In a temperature of 32° C. the oxygen unsaturation of the venous blood of 6 patients in 24 determinations was on an average 2.92 vol. per cent.  $\pm$  0.62 with a maximum of 4.38 and a minimum of 1.85, or 81.5 per cent. mean oxygen saturation.*

4. *Thus, the bright-red colour of the venous blood in the tropics is caused by the high oxygen content of this blood, as Mayer inferred a century ago.*

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## Beobachtungen über den feineren Bau und die Entwicklung der Retikulozyten.

Von

IVAR WALLGREN.

(Bei der Redaktion am 8. Mai 1943 eingegangen).

Zu den Methoden, die von der klinischen Hämatologie in Gebrauch genommen worden sind, gehört nunmehr auch die Färbung der Retikulozyten. Auf einem Objektträger, den man vorher mit einer 1 %igen Alkohollösung von Brillantkresylblau präpariert hat, lässt man einen Tropfen frischen Blutes sich unter dem Deckglas ausbreiten. Die Farbe wird von dem Plasma oder dem Serum des Blutes aufgelöst und den Blutkörperchen in ziemlich konzentrierter Form zugeführt. Ein Teil der Erythrozyten nimmt dabei blaue Farbe auf. Es wird heute allgemein angenommen, dass gerade die jugendlichsten, nicht ausgereiften roten Blutkörperchen auf diese Weise vitalgefärbt werden.

Heilmeyer teilt die Retikulozyten in folgende Gruppen:

*Gruppe 0:* Kernhaltige Reticulozyten (Normoblasten, Megaloblasten). Die vitalfärbbare Substanz liegt als dichtes Netzwerk in der Umgebung des Kerns. Diese Zellen gehören dem Knochenmark an und kommen bei Gesunden im strömenden Blut nicht vor.

*Gruppe 1:* Knäuelform. Die vitalfärbbare Substanz liegt als dichtes Netzwerk mit eingelagerten Granula in der Mitte der Erythrozyten. Sie stellen die jugendlichsten kernlosen Reticulozyten dar.

*Gruppe 2:* Netzformen. Die reticuläre Substanz hat sich aufgelockert und breitet sich netzartig über die Erythrozytenscheibe aus.

*Gruppe 3:* Unvollständige Netzformen. Die vitalfärbbare Substanz beginnt sich aufzulösen. Von dem ursprünglichen Netz sind nunmehr einzelne Bruchstücke vorhanden.

*Gruppe 4:* Ausreifungsformen. Die vitalfärbbare Substanz ist fast vollständig aufgelöst, nur mehr vereinzelte Granula oder kleinste Netzstückchen sind vorhanden. Diese Gruppe stellt das Ende des Ausreifungsprozesses dar. Durch Verschwinden der Granula gehen die Zellen unmittelbar in die ausgereiften Erythrozyten über.»

Wenn die Retikulozyten also auch in den Einzelheiten beschrieben und allgemein zum Gegenstand täglicher praktischer Untersuchungen gemacht worden sind, sind die Ansichten darüber, warum sich die jugendlichsten roten Blutkörperchen auf diese Weise färben, doch geteilt. Wird die Farbe in eine präformierte Substantia granulofilamentosa aufgenommen oder handelt es sich vielleicht nur um eine Färbung adsorbierter Partikelchen oder um eine Ausfällung des Farbstoffes? Oder bilden sich möglicherweise die färbbaren Teile der Erythrozyten durch die Einwirkung des giftigen Farbstoffes? Alle diese Fragen sind noch nicht genau beantwortet.

In der Hoffnung, einige Beiträge zur Lösung des Problems liefern zu können, habe ich die Retikulozyten einer näheren Prüfung unterworfen und gestatte mir, hier über die ausgeführten Versuche zu berichten. Diese gründen sich auf eine vom Verfasser dieser Zeilen vor kurzem veröffentlichte Untersuchung über den feineren Bau und die Funktion der menschlichen Zelle.

In den weissen Blutkörperchen konnten dabei zwei verschiedene Systeme im Plasma der Zellen nachgewiesen werden. Das eine war aktiv beweglich und bestand aus einer grauen Grundsubstanz, die zahlreiche weisse Tropfen enthielt. Das andere System war vitalfärbbar und nahm Brillantkresylblau sehr begierig auf. Es bestand aus Tropfen von etwas wechselnder Grösse, die in der Zelle von dem aktiv beweglichen System passiv hin und her transportiert wurden. Die Tropfen teilten sich oft in neue Tropfen, die von der aktiv beweglichen Substanz nach verschiedenen Seiten hin geführt wurden, wobei nicht selten ein feiner Faden zwischen ihnen entstand. Die weissen Tropfen in dem aktiv beweglichen System nahmen keine Farbe auf, erschienen aber wie leuchtende Granula in Dunkelfeldbeleuchtung. Die beiden erwähnten Systeme konnten in allen lebenden weissen Blutkörperchen nachgewiesen werden. In

fixierten Normo- und Megaloblasten, in Knochenmarkszellen und in Gewebszellen verschiedener Art waren in Dunkelfeldbeleuchtung ähnliche Strukturen zu beobachten, was darauf deutet, dass das aktiv und das passiv bewegliche System in allen Zellen des Menschen wiederzufinden sind. Da die jugendlichen Erythrozyten Brillantkresylblau aufnahmen, lag es mithin nahe, anzunehmen, dass in diesen Zellen noch Reste des passiv beweglichen Systems vorhanden seien.

Um die Richtigkeit einer solchen Annahme nachzuprüfen, wurden folgende Versuche ausgeführt.

### *Versuch 1.*

Ein für klinischen Gebrauch mit Brillantkresylblau (Merck) gefärbtes Blutpräparat aus einem leberbehandelten Fall von Wurmanämie mit 30 % Retikulozyten wird, nachdem das Deckglas mit geschmolzenem Vaseline umgeben worden ist, im erwärmten Mikroskop durchgemustert. In dem Präparat finden sich zahlreiche Retikulozyten, die zu Heilmeyer's Gruppe 1 gehören. Die Zellen sind trichterförmig, mit gefaltetem Rand. Sie erinnern in ihrer Form an Stiefmütterchen, deren Blütenkelch mit blauen Körnchen bestreut ist. Zwischen den Körnchen befinden sich stellenweise feine blaue Fäden. Bei Dunkelfeldbeleuchtung sieht man eine von leuchtenden Körnchen gebildete Granularsubstanz, die einen bedeutend grösseren Umfang als die gefärbte Substantia granulofilamentosa hat. Sie nimmt den grössten Teil der Zelle ein. Nur die peripheren Teile der Blutkörperchen sind optisch leer. Die ungefärbten Tropfen bilden ein Netzwerk, in dessen Maschen die gefärbten Tropfen sitzen. Die Ähnlichkeit mit dem aktiv und dem passiv beweglichen System in den Leukozyten ist frappant. Die älteren Retikulozyten erinnern ihrer Form nach an die reifen Erythrozyten. Man sieht in ihnen ähnlich gefärbte und ungefärbte Granularmasse wie in den eben beschriebenen Zellen, aber die Granula treten in Gruppen auf, die in der sonst strukturlosen Zelle nicht miteinander zusammenhängen. Zwischen den blauen Tropfen erscheinen einige feine blaue Fäden. Die neutrophilen Leukozyten in dem Präparat haben Farbe aufgenommen, sind aber alle bei der Untersuchung, einige Stunden nach der Herstellung des Präparates, tot. Das Präparat wurde in Zimmertemperatur aufbewahrt und wiederholt besichtigt. Noch einen Monat später waren in den Retikulozyten gefärbte Granula zu finden.

*Versuch 2.*

Von demselben Patienten wird 2 Tage später ein ungefärbtes Nativpräparat genommen und in Dunkelfeldbeleuchtung bei 37° durchgemustert. Die jugendlichsten Retikulozyten weisen viel weniger nicht färbbare Körnchen auf als im vorhergehenden Versuch. Während ein jugendlicher tütenförmiger Retikulozyt beobachtet wird, richtet sich plötzlich mit einem Ruck ein Zipfel auf. Nach einiger Zeit haben die Granula weiter an Zahl abgenommen, und als die Beobachtung nach 1—2 Stunden abgeschlossen wird, lassen die Zellen gar keine Körnchen mehr erkennen. Zugleich haben sich auch die jugendlichen Zellen ausgestreckt. In unmittelbarer Nähe der beobachteten Retikulozyten erscheinen zahlreiche leuchtende Granula in lebhafter Brown-Bewegung. Die Körnchen haben sich also nicht aufgelöst, sondern sind von den Retikulozyten abgestossen worden. Die Granulozyten sind in dem Präparat am Leben.

*Versuch 3.*

Bei derselben Gelegenheit wie im vorhergehenden Versuch entnommenes Blut wird mit gleichen Teilen Brillantkresylblau (Hollborn) 1: 10,000 gemischt und auf dem Wärmetisch des Mikroskops nach 2 Stunden untersucht. Um 13 Uhr hat ein tütenförmiger Retikulozyt zwei gefärbte Tropfen im Zentrum. Um 13.55 Uhr sind die Farbtropfen verschwunden. Um 14.10 Uhr hat sich die Zelle gestreckt und ist rund. In den peripheren Teilen der Zelle sieht man noch zwei Gruppen von Granula. Der jugendliche Retikulozyt ähnelt jetzt einer älteren Form.

In der Beschreibung des Versuches 1 wurde auf die grosse Ähnlichkeit zwischen den Strukturen in den Retikulozyten und dem aktiv und passiv beweglichen System der weissen Blutkörperchen aufmerksam gemacht. Es scheint mir daher wahrscheinlich, dass die Retikulozyten vitalfärbbar sind, weil sie Reste des passiv beweglichen Systems enthalten. In Versuch 1 war die Farbe den Blutkörperchen so zugeführt worden, dass der Objektträger, auf dem der Blutstropfen angebracht wurde, mit 1%iger Brillantkresylblau-Lösung präpariert worden war. Die Farbe wurde also den Zellen in konzentrierter Form dargeboten und wirkte wie ein zelltötendes Gift. Die Granulozyten waren in dem Präparat tot.

Man durfte daher auch annehmen, dass die Retikulozyten getötet worden waren. Aus diesem Grunde hörte offenbar auch die weitere Entwicklung der jugendlichen roten Blutkörperchen auf, und noch nach einem Monat waren in den Retikulozyten des Präparates, das in Zimmertemperatur aufbewahrt worden war, Granula wiederzufinden.

In Versuch 2, in dem ein ungefärbtes Nativpräparat zur Verwendung kam, waren die Retikulozyten aller Wahrscheinlichkeit nach noch am Leben, wie die Granulozyten in dem Präparat. In der Wärme veränderten sich die Zellen schnell. Die jugendlichsten Retikulozyten nahmen eine Form an, die an die der reifen roten Blutkörperchen erinnerte, und die Granularsubstanz wurde abgestossen, während die Zellen beobachtet wurden.

In Versuch 3 färbten sich die Granulozyten, aber die Farbe wurde den Zellen in stark verdünnter Form zugeführt. Durch zahlreiche Versuche mit derselben Farbe (Brillantkresylblau Hollborn) habe ich mich überzeugt, dass auf diese Weise gefärbte Granulozyten mehrere Stunden nach der Färbung leben können. Man könnte daher annehmen, dass die Retikulozyten bei diesem Versuch zur Zeit der Beobachtung auch am Leben waren. Auch jetzt entwickelten sich die gefärbten Retikulozyten in der Wärme. Hierbei stiessen sie ihre Granula ab, und die jugendlichsten Formen gingen in ältere Entwicklungsformen über. Das stimmt völlig mit ähnlichen Erscheinungen bei den neutrophilen Leukozyten überein. Sowohl die vitalfärbbaren Tropfen als die nicht färbbaren in Dunkelfeldbeleuchtung sichtbaren Körnchen bleiben, wie aus meinen noch unveröffentlichten Untersuchungen hervorgeht, noch lange nach dem Tode der Zelle erhalten. Sie lösen sich dabei nicht auf, können auch von der Zelle abgestossen werden.

Die Befunde, über die hier berichtet worden ist, stehen mit früheren Beobachtungen über die Retikulozyten im Einklang: Nach dem Tode verschwinden die Retikulozyten schnell aus dem Blute (Hertz, Krafka), aus dem Blute des toten Fetus schon innerhalb 24 Stunden; in Blut, das *in vitro* aufbewahrt worden ist, findet man nach 1—2 Tagen keine Retikulozyten (Dencke); wird das Blut dagegen im Eisschrank gehalten, so können Retikulozyten noch nach einem Monat nachgewiesen werden (Nittis); Wärme beschleunigt also die Entwicklung der Retikulozyten, während Kälte sie lähmt.

In meiner obenerwähnten Untersuchung über den feineren Bau



## REVUE DES LIVRES.

*G. Domagk and C. Hegler: Chemotherapie bakterieller Infektionen.* 327 pages. Price in carton reichsmark 14: —. Hirzels Verlag, Leipzig, 1942.

Domagk and Hegler's work »Chemotherapie bakterieller Infektionen» has appeared in a new and revised edition. Domagk is responsible for the experimental part, Hegler for the clinical.

In the first seven chapters Domagk gives an excellent description of the development of chemotherapy, from prontosil to the latest achievements in that field: the preparations marphanil, tibatin, amonal, etc.

A large number of comparative tests have been made of the effect of different preparations on one and the same bacteria strain. As an example of these experiments, the following may be adduced: A strain of  $\beta$ -hemolyzing streptococci was injected into mice, and the effect of different preparations on the infection were studied. Of 14 control animals which received injections of the above mentioned bacteria, all were dead after 48 hours. After the same period 12 out of 20 animals treated with sulphanilamide had survived, 16 out of 20 treated with sulphapyridin, 10 out of 20 treated with sulphathiazol, and all the 20 animals treated with tibatin (galactoside of diaminodiphenylsulphon). This series of experiments, and others, also appear to indicate that the new Igefa preparation tibatin is particularly valuable. Above all it appears to surpass other chemotherapeutics in cases of puerperal sepsis.

In the case of anaerobic infections, marphanil appears to have a better effect than earlier preparations. It differs from sulphanilamide mainly in that a methyl group appears between the amino

preferred. The interval between the doses should not be longer than 4—8 hours.

In a couple of chapters the resorption and excretion conditions and the toxicology of the sulphanilamide preparations are discussed.

As is mentioned above, Hegler has worked up the clinical part of the work. He stresses anew the excellent effect of prontosil on erysipelas. In the case of endocarditis lenta he discusses, *inter alia*, the interesting circumstance that, at times, chemotherapy has a greater effect if hyperthermia is present. Lichtman and Bierman (New York) have collocated about 800 cases of endocarditis lenta, of which between 200 and 300 were treated with sulphanilamide preparations. Two series, in which hyperthermia treatment was employed simultaneously with chemotherapy, showed the best results. In one series hyperthermia up to c. 40° (5 hours heating or longer every third day) was induced physically, and 16 % of cures were obtained. The other series, in which hyperthermia was brought about by means of intravenous injections of typhus or paratyphus vaccine, showed a still higher percentage of cures. The author points out that the series is small, but of the greatest interest.

As has been pointed out above, it seems that tibatin has a specially favourable effect in cases of puerperal sepsis.

Hegler has not carried out any detailed tests with staphylococcus infections, but seems to share the prevalent opinion that sulphathiazol is probably the most efficacious preparation.

The author has mainly employed uliron for gonorrhea and stresses the fact that this treatment gives excellent results. Of other preparations he calls attention particularly to sulphathiazol and sulphapyridin.

Hegler considers that at the present time sulphapyridin is the best preparation against meningococcus meningitis. Good results have also been obtained with chemotherapy in cases of influenza-bacillus meningitis.

Hegler emphasizes the great advances which have been made with regard to the treatment of pneumonia, thanks to the discovery by Whitby, Evans and Gaisford of the effect of sulphapyridin. During the period October 1938—March 1941, Hegler treated 730 cases of pneumonia with sulphapyridin at St George's Hospital,

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HANS ØDEGAARD, 1942.

*J. Scheel.*

## Paroles d'adieu prononcées à la mémoire d'Olaf Scheel le 19 janvier 1943

devant la Société de Médecins Suedois.

Par

G. BERGMARK.

(Ce travail est parvenu à la rédaction le 12 Avril 1943).

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Au début de janvier, cette année, nous apprenions de Norvège qu' Olaf Scheel, ancien médecin-chef de l'hôpital d'Ullevål et Membre Etranger de notre Société, était décédé le 27 décembre. Avec lui disparaît l'un des médecins les plus distingués de Norvège et l'un des plus ardents champions de la collaboration scandinave.

Né en 1875, étudiant en 1893, med. cand. en 1900 et docteur en 1912, Scheel se consacra d'abord à l'anatomie pathologique et il fut pendant plusieurs années l'assistant de Harbitz. Bientôt, cependant, il fut attiré par l'étude des maladies internes et devint le disciple de Sören Laache et de Peter Holst. Interne des hôpitaux en 1907, médecin attaché à l'hôpital d'Ullevål en 1912, il prit en 1915 la direction d'un service à cet hôpital. En 1919, il fut nommé professeur de clinique médicale et il assura cette double charge jusqu'à sa retraite en 1940. Il fut Président de la Société de Médecine de 1934 à 1936 et Président du dernier Congrès Scandinave de médecine interne en 1939 à Oslo.

Scheel laisse après lui des travaux scientifiques nombreux et variés. Ses premiers travaux ont trait surtout à des questions d'anatomie pathologique, telles que les altérations du système vasculaire au cours des diverses maladies, la pathogénèse de l'ictère et l'histopathologie de la poliomyélite. Parmi ses travaux cliniques,

on remarque surtout sa grande étude *Der klinische Blutdruck* 1912, où il démontre — le premier, autant que je sache — qu'on peut constater de l'hypertension sans que les reins révèlent la moindre altération anatomique visible au microscope. En outre, il a fourni des contributions importantes au diagnostic des maladies de l'estomac et du foie ainsi qu'à l'étude clinique du diabète. Mais le domaine qui, durant ces 15 dernières années, accapara par-dessus tout son attention, et où il a apporté une contribution capitale, c'est celui de la tuberculose pulmonaire, de sa clinique, de son caractère épidémique et de sa prophylaxie.

Scheel ne s'en laissait pas imposer par les résultats que la lutte contre la tuberculose peut étaler jusqu'ici. Cette lutte, comme on le sait, a été principalement conduite comme un combat contre la contagion. Dans une maladie infectieuse aiguë, on peut enrayer la contagion par l'isolement des malades. Il en est de même pour une maladie chronique sporadique telle que la lèpre. En ce qui concerne la tuberculose, considérée seulement en Norvège, où l'on peut, comme l'indique Scheel, malgré les nombreuses constructions de sanatoriums, pourtant à peine réussir à isoler un cinquième des cas infectieux, dans ce cas, la question se pose tout autrement. Cette lutte, en vérité, n'a pas atteint son but, puisque, même dans un pays à la population clairsemée comme la Norvège, tous les individus pratiquement présentent des signes d'infection tuberculeuse avant d'atteindre l'âge de trente ans. Si l'on réussit à protéger effectivement l'enfance, ceux qui traversent la crise de la puberté et les adolescents n'en sont que plus exposés. En ce qui concerne l'adolescence, Scheel n'a pas pu constater la moindre diminution de la mortalité par la tuberculose. En d'autres termes, pour citer Scheel lui-même, celui qui a réussi à éviter Charybde dans l'enfance, rencontre Scylla à l'âge de la puberté ou plus tard, et il est plus que douteux qu'on ait affaire, en ce qui concerne les filles, à une mortalité moindre pour celles qui sont contaminées au cours de leurs dernières années scolaires que pour celles qui le sont au cours des premières années scolaires.

S'appuyant sur des épreuves très poussées fondées sur la méthode de Pirquet, Scheel se sépare nettement de la théorie généralement admise qui affirme que la mortalité par la tuberculose dans la deuxième partie de la jeunesse dépendrait du réveil d'une infection tuberculeuse latente existant depuis l'enfance. Il souligne avec force

que l'infection déterminante de la tuberculose et l'apparition de la maladie, ainsi que son évolution qui peut être fatale, constituent en règle générale, des phases qui se suivent rapidement.

Scheel a constaté une corrélation entre l'accroissement de la taille des soldats et la diminution de la mortalité par la tuberculose. Il voyait là une confirmation de son idée que la cause essentielle de la diminution de la mortalité par la tuberculose ne devait être cherchée ni dans la lutte contre la contagion, ni dans les soins sanatoriaux, mais tout simplement dans l'amélioration des conditions économiques et l'élévation du niveau de la vie.

Cela nous rappelle un mot qui fut prononcé dès 1907 par l'un de nos pionniers suédois de la lutte anti-tuberculeuse, le vieux docteur Carl Waller, de Hålahult: «Ce ne sont pas les sanatoriums mais les syndicats qui font diminuer la mortalité par la tuberculose.»

L'apport scientifique de Scheel, celui qui peut sans doute être considéré comme le plus important de sa carrière, ce sont ses recherches — poursuivies et achevées depuis si élégamment par Heimbeck — concernant les risques de contagion encourus au cours de leur travail dans des services de tuberculeux par les étudiants en médecine et les infirmières, selon que leur Pirquet est négatif ou positif.

Les chiffres apportés par Scheel démontrent de la manière la plus convaincante que, de ces deux catégories de jeunes gens, ceux qui, d'après le résultat de la réaction de Pirquet, doivent être considérés comme ayant échappé à une infection tuberculeuse antérieure, sont ceux qui sont le plus exposés à la tuberculose, beaucoup plus que ceux qui présentent des signes d'une infection antérieure.

Ce fait une fois constaté, Scheel se consacra à une étude plus approfondie de la valeur prophylactique de la vaccination par le B. C. G. Malgré son scepticisme habituel, il fondait sur cette méthode de grandes espérances, et on peut le considérer, dans ce domaine, comme un précurseur dans les pays du Nord.

C'est à cette question qu'est consacré son dernier article dans le *Nordisk Medicinsk Tidskrift*, où il peut faire état de vastes matériaux portant sur des cas suivis pendant longtemps et qui montrent que la mortalité par la tuberculose peut être considérablement réduite grâce au B. C. G. Mais il fait une importante réserve sur la portée de la méthode, à savoir que la protection conférée par la vaccination ne peut guère durer plus de quatre ou cinq ans.



Lorsque Scheel, il y a quelques années, s'adressa ici même aux médecins suédois, c'était justement pour leur parler du vaccin de Calmette.

Un des plus beaux titres de gloire que se soit acquis Scheel, c'est la magnifique description de la tuberculose qu'il a donnée dans le *Nordisk Lärobok i intern medicin*.

Toutes les publications de Scheel sont empreintes d'un accent sobre et véridique. Il n'a jamais laissé publier un travail inachevé. L'attitude critique que l'on distingue dans toutes ses publications scientifiques, se retrouvait aussi dans son activité pratique. Il se montrait particulièrement critique en ce qui concerne l'action des préparations pharmaceutiques; par exemple, il montrait une grande répugnance devant l'emploi, accepté sans discernement tant par le public que par les médecins, des remèdes contre la toux qui facilitent l'expectoration. Il a émis l'opinion que ces remèdes n'agissent que lorsqu'on «les administre à un stade où l'expectoration devient d'elle-même plus aisée; mais, alors, il est superflu de les prescrire».

J'ai dit que Scheel était un partisan ardent de la collaboration entre les pays du Nord. Il était l'hôte assidu de nos congrès, et, en qualité de secrétaire général, il a accompli une tâche considérable et fort utile. Lorsqu'après la crise de 1905, les congrès médicaux reprirent, en 1909, il y joua, malgré sa jeunesse, un rôle très actif. Il fut le président hautement apprécié et chaudement acclamé du dernier congrès, en 1939, à Oslo.

Personnellement, Scheel était un être exceptionnellement attirant. Sans prétention, d'une culture raffinée, compétent dans beaucoup de domaines, et non pas seulement en médecine, il était le compagnon de voyage rêvé. Bien qu'il eût de la vie et des hommes une conception sceptique, quelquefois pessimiste, il avait un sens profond de l'humour. Ceux qui ont assisté au Congrès de Copenhague, en 1927, se souviennent peut-être des paroles qu'il prononça, lorsqu'il se chargea d'exprimer les remerciements des hôtes: «Nous avons été si bien reçus et entourés de tant d'attentions, que je voudrais dire comme cette femme qui contemplait le groupe du sculpteur Sinding *To Mennesker*: «Si une chose comme ça finit bien, alors tout finira bien!»

Patriote ardent, il a souffert au-delà de toute expression des malheurs qui sont venus accabler son pays, mais il ne s'est pas laissé abattre. Dans une lettre à un collègue suédois, il disait: «La

situation ici n'est pas la même pour tous. Pour ma part, je ne puis pas me plaindre, du point de vue matériel. J'ai la chance d'habiter un appartement muni d'un vieux poêle et si démodé que personne ne veut l'occuper; je chauffe seulement le petit bureau où je vis. La difficulté principale est d'arriver à me procurer un peu plus de bois que je n'en ai, sinon je mourrai de froid cet hiver.

Cette lettre était datée du 24 décembre. Le matin du jour de Noël, il tombait inanimé dans la rue et il mourait le 27 décembre.

La lettre dans laquelle le vieil ami de Scheel, compagnon de sa jeunesse, le professeur Olav Hanssen, annonçait sa mort, se terminait par ces mots: «Grieg écrivait un jour: 'Dans la jeunesse, avoir des amis est chose naturelle; dans la vieillesse, nous comprenons de quel prix ils sont'. Scheel était de ceux dont la possession n'a pas de prix.»

Dans cette époque difficile, Scheel s'est affirmé comme une des figures de premier plan de la médecine nordique.

Au nom de la Société de Médecins Suedois, je salue respectueusement sa mémoire.

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From the St. Elisabeth-hospital, Tilburg, Holland.

## **Sharp Penetrating Heart Wounds.**

By

**Dr. F. S. P. van BUCHEM.**

(Submitted for publication April 15, 1943).

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The purpose of this article is not to follow up the surgical problems which arise in case of a sharp heart wound, but is rather a study of the consequences, which this causes on the circulation, and especially on the heart itself.

We had the opportunity of observing a case of sharp heart wound from the 1st day after the trauma. A man of 26 received, on the 10th day of October, at 10 o'clock, a stab in the cardiac area. He walked on 150 meters, then fell. After about 15 minutes, a first aid bandage was applied and he was transported to the hospital. At this time the man was suffering from shock. The skin was clammy and cyanotic. The pulse was faint, irregular and unequal. Above the heart a murmur could be heard, and the sounds were almost inaudible. On the left side were signs of a pneumothorax. At the height of the 9th rib was a wound in the medioclavicular line, out of which appeared much blood and clots. The operation took place within an hour after the wounding, under laughing gas narcosis with surcharge. The operator, (Dr. Goossens) found a wound 8 cm long in the pericardium, and a wound of several centimeters' length near the base of the heart, through the wall of the right ventricle. Blood came in spurts out of the penetrating heart wound. The myocardium and the pericardium were sewn up, as well as the pleura. None of the coronary arteries needed to be ligated.

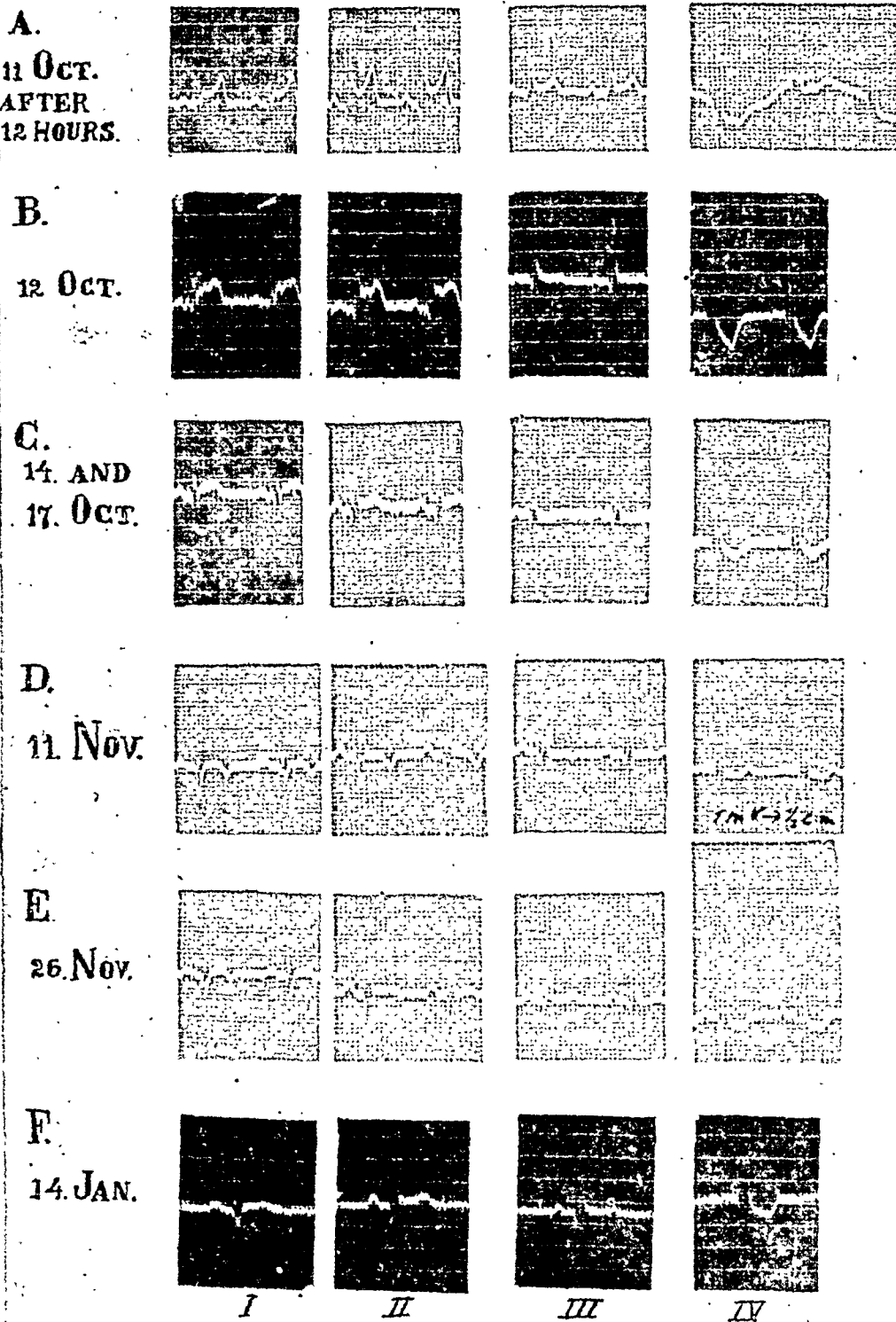


FIG. 1.

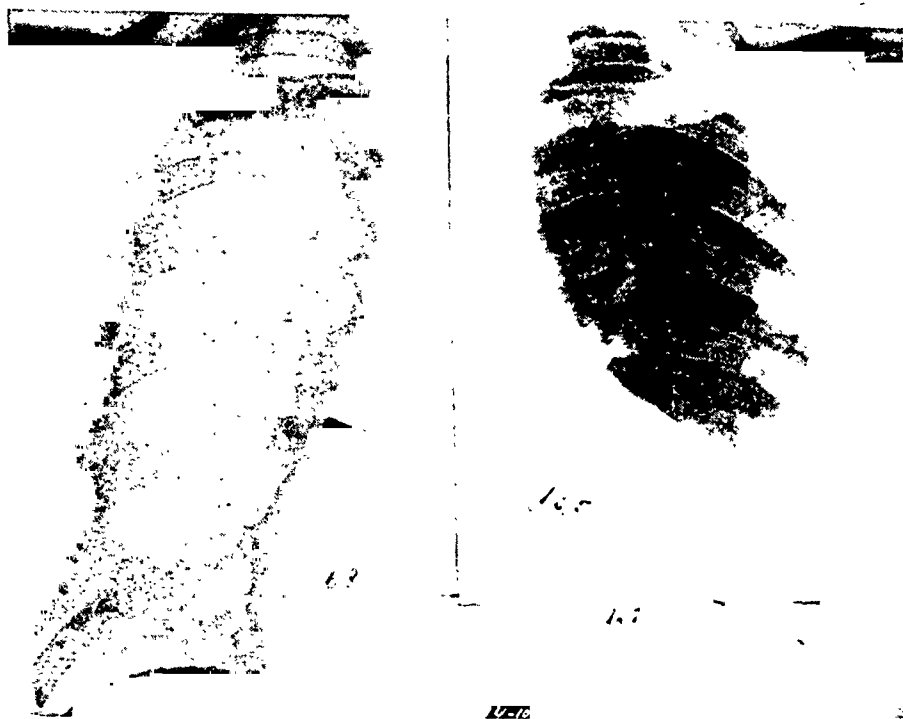


Fig. 2. X-ray photo 14 October. L. 18.5 cm. Mr. 6.8 cm, Ml. 12.1 cm.

About 12 hours after the trauma, the general condition was rather good. The pulse was frequent, 116 per minute, regular, moderately filled. The blood pressure was 95/65. The heart figure proved to be somewhat dilated. The sounds were clear and no pericardial friction was heard. In the lower left side at the back, many damp râles were audible. The liver was not palpable and the bipercussion was not enlarged. The urine was free from albumen, the urobilin reaction was clearly positive.

The electrocardiogram then already showed decided anomalies (fig. 1 a), namely a displacement of the S—T-segment above the isoelectric line in all of the three standard leads, in the 1st lead 2 mm, in the 2nd lead 3 mm, and in the 3rd 1 mm. Temperature rose the 1st days to 38.2 (armpit). Sedimentation was 75 mm, after 1 hour. Haemoglobin percentage was 85, erythrocytes 3,500,000, leucocytes 8400, eosin. 1 %, segment nuclear 78 ½ % lymphocytes 12 ½ % monoc. 7 ½ % plasma cells ½ %.

On the 4th day pericardial friction sounds were present. The liver was not palpable. X ray photos fig. 2 showed the heart

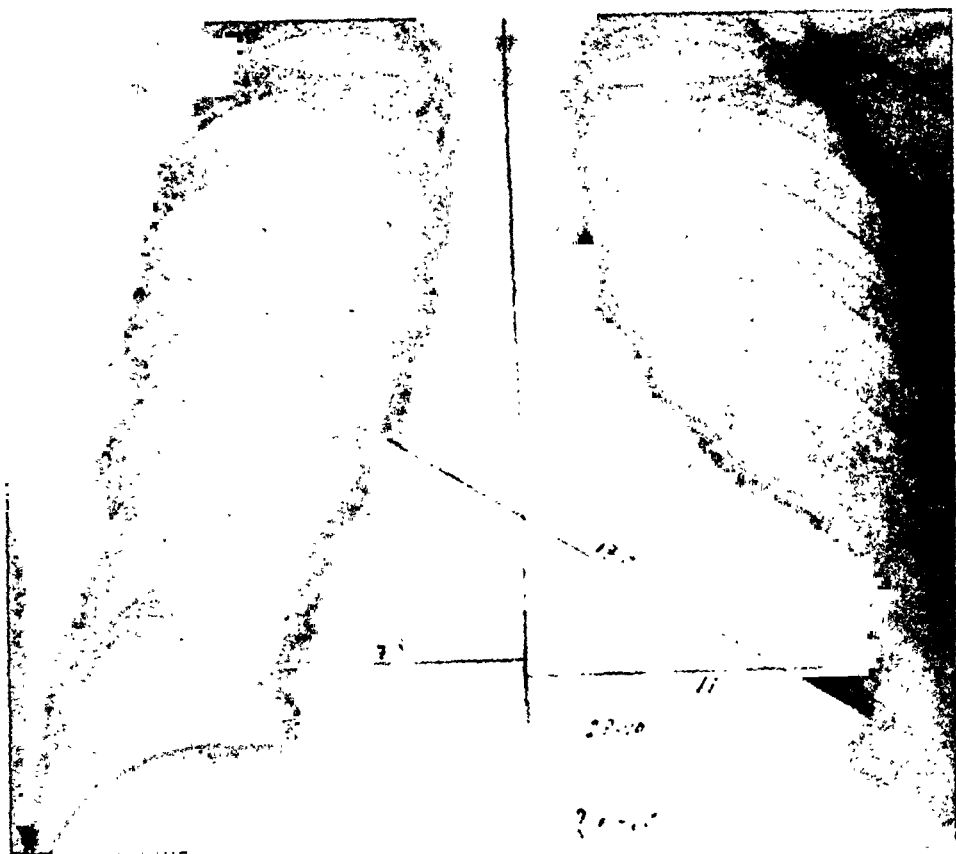


Fig. 3. X-ray photo. 28 October. L. 17.5 cm.

shadow strongly broadened on both sides, the pulsations of the borders were slight, but the contours of the various parts were quite visible. An exudate of any significance was not to be seen. The pleura anomaly is responsible for the fading on the left under side, an obvious effect of the wound. After 7 days the heart figure seemed decidedly smaller but still thick. The electrocardiogram showed a gradual receding of the defects (fig. 1 b and 1 c).

10 days after the trauma the venal pressure was still too high (140 mm) the circulation tempo normal (fluoresceine 20/25 sec.) The pericardial friction was still audible as well as crepitating râles in the left lower side at the back. The liver was not palpable and not enlarged percutorically.

18 days after the trauma the patient felt well, and was not tired. The heart seemed still broadened however, but no defects were to be heard, namely no pericardial friction and no gallop-

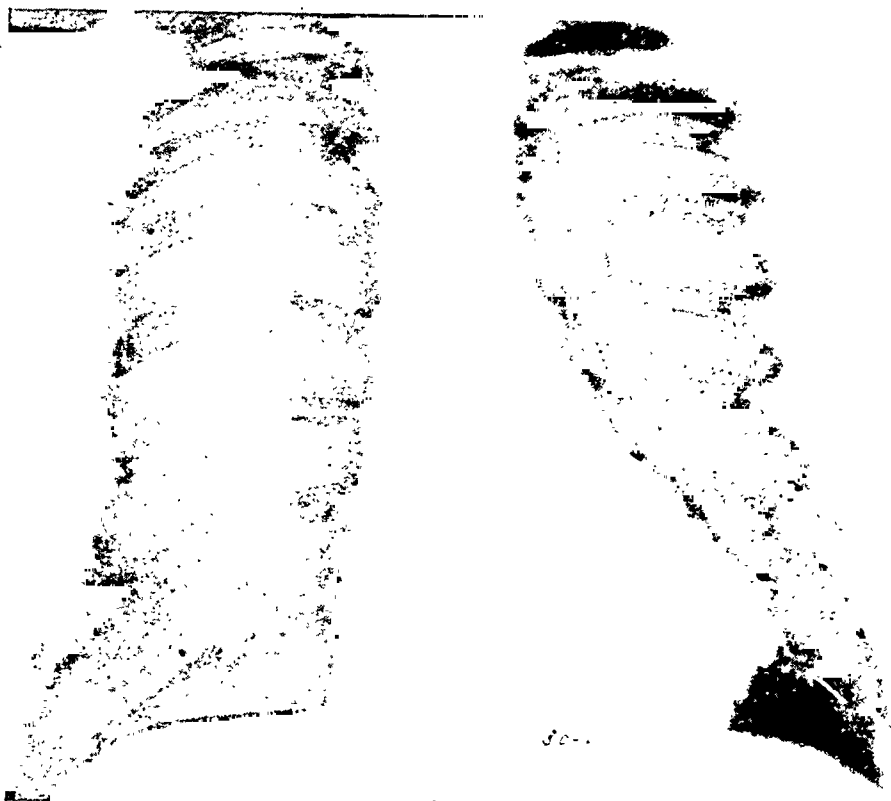


Fig. 4. X-ray photo 30 November. L. 16.1 cm. Aneurysma cordis (T).

rhythm. The sedimentation tempo showed 125 mm, after 1 hour. A strong urobilinuria was present. Blood pressure 125/80. X ray photo showed a thick heart shadow with a ragged border near the apex (fig. 3). The electrocardiogram still showed only a negative T in the 1st and 2nd leads and an upward directed convex ST-segment.

Exactly a month after the trauma the patient was doing well. He felt a thrust from time to time in the cardiac area. The pulse was regular, well filled. Blood pressure 115/70. The ictus cordis was palpable in the medioclavicular line. The heart figure reached percutorically from the right sternal border to the medio clavicular line. The sounds were clear. The liver was not palpable. The sedimentation tempo stood at 18 mm. Now the heart, from x-ray photos, proved to be decidedly smaller. Next to the apex cordis could still be seen a slight bulge on the heart shadow (aneurysma

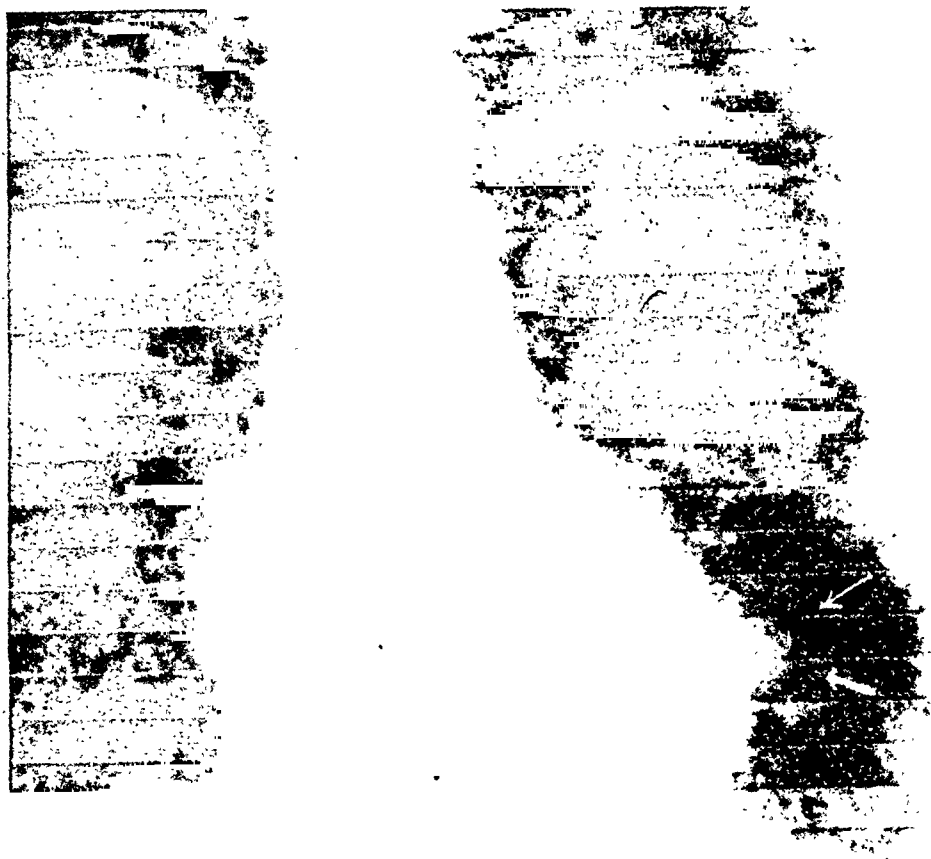


Fig. 5. Kymogram, absence of pulsation at the height of the aneurysma cordis.

cordis). The electrocardiogram showed a negative T in the 3 standard leads (fig. 1 d).

1 ½ months after the trauma the general condition was good. Patient still coughed up slime. He smoked a great deal. The pulse was regular, equal, frequency 84 per minute. Blood pressure stood at 100/60. During the physical examination no defect in the heart was to be found. Some bronchial murmurs above the lungs were audible. The liver was not palpable. The urine was free of albumen, having only a very small amount of urobilin, sedimentation tempo showed 2 mm after 1 hour, circulation tempo showed with the saccharine method 10", with the fluoresceine method 25/30", the venal pressure 115 mm, vital capacity 3 ½ liter (length 1.71 m, weight 75 kg).



The x ray (fig. 4) showed the heart to have a normal size, but a slight bulging of the heart shadow could be seen near the apex.

The electrocardiogram still showed a negative T in the first lead (fig. 1 e). After 3 months the only defect showed by electrocardiogram was a slight displacement of the S—T segment in the 2nd lead (1 mm) and a still rounded ST—T in the 4th lead (fig. 1 f).

We have even checked up with a kymogram, where the absence of pulsations at the height of the wound was clearly visible (fig. 5). The reactions of Wassermann, Kahn and Meinecke were negative.

The symptoms accompanying a sharp penetrating heart wound are usually kept under control by the existing shock, resulting from the loss of blood. In addition the effects of an eventual heart tamponade (swollen neck arteries) can appear. The pulse is faint, often irregular. The heart sounds are weak, sometimes hardly audible; murmurs were heard several times. Blood pressure is low, below the 100 mm. If the liver is touched in the wounding, the bleeding is usually deadly, if proper assistance is delayed. Mortality in operations gives contrasting figures (26—60 %). The prognosis is favorable if the sewing-up of the heart wound is expertly done, no matter if the former condition was deplorable. In case the larger branches of the coronary arteries must be ligated, the fact is for the prognosis is unfavorable. It will then be necessary, usually, to make new collateral connections, a heart lung suture for example, although some cases without this extra operation are known to have been successful [Schneider (14).]

On the long run the results prove satisfactory, although the heart muscle acquires a scar, at the place of the heart wounding. Usually the patients are able to resume their work as before.

If one of the large branches of the coronary arteries is ligated, an unfavorable course can *later* be remarked. For example, Mohr (7) saw in his patient, in whom the ramus descendens of the art. coron. sinistra was ligated and where a good result was established according to a normal electrocardiogram, after 4 years a dilatation of the heart with a pronounced defect shown in the electrocardiogram (in the 1st lead Q strong, T negative, ST above the isoelectric line).

The wounding in our case, was of a young man, who had never been ill. He had 3 healthy children, his wife was also healthy and had had no miscarriages, the reactions on lues were negative.

Among the cases reported in medical literature, such defects in the electrocardiogram consisted in a shifting of the ST-segment above the isoelectric line in the 1st and 2nd leads, combined with a saddle form. In our patient a similar defect showed itself in the 3rd lead, which we were able to record, as the electrocardiogram could be controlled already 12 hours after the trauma [Davenport and Markle (3)], on the following day the ST segment in the third lead was almost on the isoelectric line again. Like others writers, we also saw the ST segment in the 1st and 2nd leads gradually approach the isoelectric line and this combined with a sharp negative T. The ST-segment showed thereby a change from the saddle form into an upward convex curve. In the thoracal lead (IV) Q remained, just as Davenport (3) and Erkelens (17) found it, but in contrast to what these examiners found, there was no question of an inversion of T in this lead. This was only shown in one cardiogram (fig. 1 d). Elkin and Phillips (5) electrocardiogrammed just before and 10 minutes after the operation, and no defect of any importance was to be seen.

When the described electrocardiograms are compared, this resemblance is striking, in spite of the difference in localization of the heart wound namely if the right ventricle [Porter and Bigger (13), Davenport and Markle (3), Wood (16), Gissane (6) our case] — or the left ventricle [Merkel (7), Erkelens (17), Bates and Talley, Elkin and Phillips (5), 2nd case), or both ventricles [Mondry (9)], were affected. If the larger branches of the artt. coronariae are ligated, then the electrocardiogram changes enough, to give a greater resemblance to the figure of a myocardium infarction (discongruence of the ST segment in the 1st and 3rd leads (Elkin and Phillips, Davenport, Blumenthal and Cantril (4)). Also no difference was to be seen whether or not tamponade of the heart was present, which Davenport, Markle (3) and Wood (16) regarded as the cause of electrocardiographic defects. Using these proofs as a base, eventual heart tamponade can be excluded as the cause of the electrocardiographic defects, and it is even less probable that the heart wound can be localized with the help of the electrocardiogram, which Merkel (7) and others contended. At first the electrocardiographic defects seemed to resemble the picture which, in case of a myocardium infarction can be seen; namely, the initial displacement of the ST-segment above the isoelectric line and the later

appearing sharp negative waves (T). Upon closer study, however, greater differences prove to exist. In the first place the upward movement of the ST-segment is combined with a saddle form, in contrast to the convex curve which appears in case of a myocardium infarction. In the 2nd place, it is clearly seen in our case, that this movement takes place in all 3 of the standard leads, in the same direction, while we see the opposite in the 1st and 3rd leads in the case of the infarction. There, the movement of the segment is upward, in the 1st or 3rd lead, combined with a depression of the ST-segment in respectively the 3rd and 1st lead.

Thirdly, the thoracal lead does not show the typical anomaly of Q on T of a case of an infarction. In our case, we see the stability of the initial Q and an absence of an inversion of T, which is so characteristic in the case of infarction of the anterior surface. Finally, in most cases, the appearance of Q in the standard leads was lacking, in the stadium of the negative T-waves. In our case however, this is true.

The differences mentioned render it therefore superfluous to seek any resemblance to a myocardium infarction.

The electrocardiographic changes, which occur in the further course, namely the sharp negative T curves, combined with a convex ST-segment especially in the 1st lead strongly resemble that which is observable in the later phases of a myocardium infarction. The distinction is that a negative sharp T in *all* 3 standard leads is not explained by a myocardium infarction, but is a characteristic of acute pericarditis [Winternitz, Langendorf (15), Noth Barnes (12), and others]. We will return to this later.

The electrocardiographic picture shows a much more striking resemblance, also in the first days, to that which is sometimes apparent with an acute pericarditis within the 1st 12 days

Vander Veer, Norris (11), Bellet and McMillan (1) found that the anomalies were clearest if an extensive subpericardial myocarditis was present. Parallelism existed even between the myocarditis and the grade of the electrocardiographic anomalies. [Bellet and McMillan(1)]. At the same time it was proven that the greater or smaller quantity of exudate was unimportant in regard to these anomalies.

• There also, do we see the typical saddle form of the ST-segment situated above the isoelectric line and a later appearance of sharp

negative T-waves. Here too the initial result of QRS in the 4th lead is stabilized, and a descent of the ST-segment in this lead is often present. (Bellet and McMillan).

When there is so much moisture in the pericardium that the pressure there becomes higher than that in the auricles, so that the auricles and the ventricles are insufficiently filled, then the coronary circulation is disturbed and consequently anomalies are caused in the electrocardiogram.

In full accordance with these researches, which clearly show that besides the pericarditis the myocardium defects are important in causing the electrocardiographic defects, are the observations in patients with a penetrating heart wound. In these case the described electrocardiographic defects are strongly pronounced, even if no branch of the artt. coronariae is touched. Winternitz and Langendorf believe that especially the pericarditis causes the changes in the electrocardiogram, otherwise such great areas of the myocardium ought be eliminaed that the patient cannot be expected to survive. That such a knife wound can cause such extensive myocardium changes is shown in the series of x ray photos, which we made of our patient. Here we can see that, firstly, the shape of the heart shadow is not determined by a pericarditis exudate, but, by a general enlargement of the heart itself, this is made clear by the form of the heart shadow with the still visible borders of the various parts and the lack of a broadening of the artery shadow.

We see the typical, plump heart form, which is sometimes to be observed in heart dilatation in case of anaemia, myxoedema, and acute myocarditis. Also, in these cases, the receding of a clear dilatation can be observed within a short time, if it concerns patients with an otherwise normal heart. (Van Buchery and Polak Daniels).

That an infected wound in an area containing such a quantity of blood and arteries as the heart muscle can be the cause of a quickly spreading inflammation is not to be wondered at.

We believe also, that this observation is a confirmation of the theory maintained by Vander Veer, Norris, Bellet, and McMillan that besides the pericarditis, especially the myocardium injury is responsible for the important, electrocardiographic defects.

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## Auricular Flutter and Auricular Fibrillation with complete Auriculo-ventricular Block.

By

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(Submitted for publication May 13, 1943).

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During the last 4 years 3 cases of auricular flutter with complete auriculo-ventricular block have been observed in »De Gamles By», and as the subject does not seem to have been treated before in the Scandinavian literature an account will here be given of these cases, and of four cases of auricular fibrillation with complete auriculo-ventricular block which have been observed within the same period.

### Previous Cases.

A combination of auricular flutter with complete auriculo-ventricular block rarely occurs. Thus Willius (1927) (8) only found it in one patient among more than 40,000, and on reviewing more than 20,000 electrocardiograms Digregorio and Crawford (1939) (1) found only 2 cases.

A survey of the cases reported up to 1937 is found in a paper by Jourdonais and Mosenthal, (3) who collected 28 cases and added a new one. Later on Digregorio and Crawford (1) published 2 more cases.

Of these 31 previous cases 4 occurred in women. The age of the patients ranged from 13 to 74 years, but 80 % were over 50 years old.

In most cases the etiology was coronary sclerosis. 3 cases were due to syphilitic heart affections, 1 to rheumatic fever, 1 to congen-

ital heart disease, and 1 to thyreotoxicosis. Most of the cases were of spontaneous origin, but three were caused by digitalis, and in two cases auricular flutter occurred with pre-existing complete auriculo-ventricular block after treatment with atropine.

In eight cases sinus rhythm was established by treatment; in five with quinidine, in 2 with digitalis, and in one by thyroidectomy. This interesting case was communicated by Strauss (1927. Reported by Gager) (2). The patient was a woman who for many years had suffered from a complete auriculo-ventricular block (congenital?) and in whom auricular flutter occurred simultaneously with symptoms of hyperthyroidism. After thyroidectomy her auricular flutter ceased, whereas the block persisted.

A combination of auricular fibrillation with complete auriculo-ventricular block is mentioned by several authors [Wenckebach and Winterberg (1927) (7), Katz (1941) (4), Scherf and Boyd (1941) (6)] as not rarely occurring, but is not more fully discussed. There does not seem to be any fundamental difference between complete auriculo-ventricular block with auricular flutter and with auricular fibrillation and in the present work therefore the two groups will be treated under one head.

### Own cases.

*Case 1.* (J. 1461/40). — Woman aged 75. Admitted 12/10—38, died 16/12—40. No previous diseases of importance. The heart affection had begun a couple of years before admission with attacks of angina pectoris followed by functional dyspnoea and retrosternal pain. Three times treated in hospital, the diagnosis being arteriosclerosis, myocardial degeneration, heart block. Electrocardiograms taken in May and September 1938 showed complete A—V block. Moved to »De Gamles By» 12/10—38. Upon admission symptoms of severe heart disease: dyspnoea and cyanosis upon the slightest exertion. Peripheral arteries very sclerotic. Pulse 36, regular. Blood pressure 170/60. The heart: Ictus in 5th intercostal space in the anterior axillary line. Over the whole precordium, most marked at the apex, a systolic blowing murmur. Action 36 as in pulse. There is pulmonary stasis and enlargement of the liver. No ascites, edema, or albuminuria. W. R.: 0. *Electrocardiogram* 14/10—38 (Fig. 1): Instead of P-waves are seen, most plainly in Lead III, regular uniform F-waves with a frequency of 375. Ventricular action regular without relation to the F-waves. Initial complexes wide (0.16), slurred. The greatest deflection upright in Lead I, negative (S-type) in Leads II and III. Deflections large. S—T<sub>1</sub> lowered. S—T<sub>3</sub> elevated. T<sub>1</sub> diphasic, T<sub>2</sub> and T<sub>3</sub> positive. — During the further

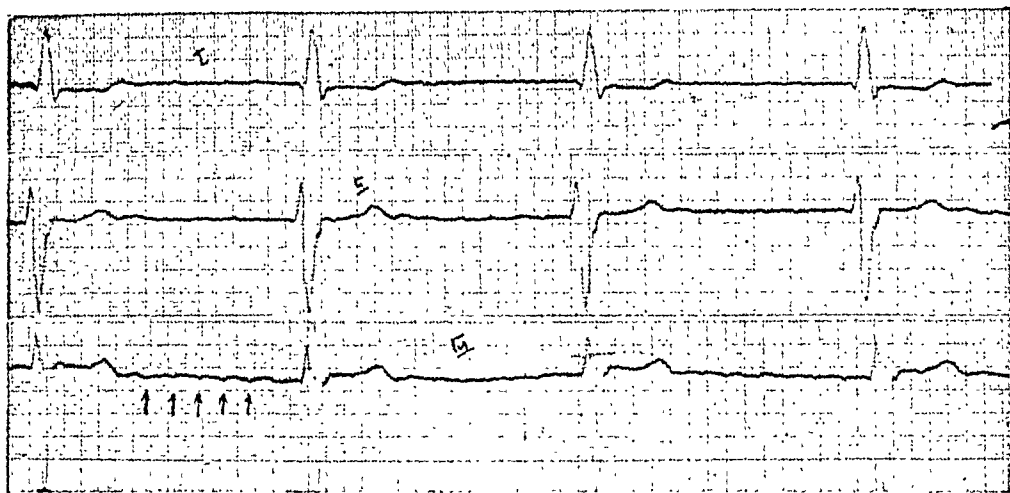


Fig. 1. Case 1, 14/10—38. Auricular flutter and complete auriculo-ventricular block.

course the pulse was constant around 36 (32—48). The patient was always somewhat dyspnoeic but managed to be up and about a great part of the time. Treated with aminophyllin. Repeated electrocardiograms all showed flutter and complete A—V block as on admission, while the ventricular complexes following clinical exacerbation presented changes indicating posterior wall infarction, and likewise revealed alterations as in bundle-branch block of the Bayley type, with a deep and broad  $S_1$  and M-shaped  $CF_2$ . Death supervened suddenly 26 months after admission. No post-mortem.

*Epicrisis.* In a woman aged 75 suffering from arteriosclerotic heart affection and in whom complete A—V block has previously been ascertained, spontaneous auricular flutter sets in. During the course of the disease the ventricular complexes are changed and show signs of posterior wall infarction and bundle-branch block of the Bayley type. The patient dies 26 months after auricular flutter has been demonstrated.

*Case 2.* (J. 161/41). — Male aged 84. Admitted 10/12—36, died 4/2—41. The only information of previous affections is of a febrile bronchitis about 10 years before the admission. The heart disease manifested itself in dyspnoea, a tendency to edema, and mild precordial symptoms in connection with a febrile bronchitis. Committed to hospital on 28/11—36, whence it is communicated that the diagnosis was senile decay, myocardial degeneration, heart insufficiency. Treated with digitalis and moved to «De Gamles By» after 12 days. — Upon admission no cyanosis or resting dyspnoea. Peripheral arteries sclerotic. Pulse 60, regular. Blood pressure 140/75. Heart covered by lung. Ictus not felt. Sounds distant, dull. No



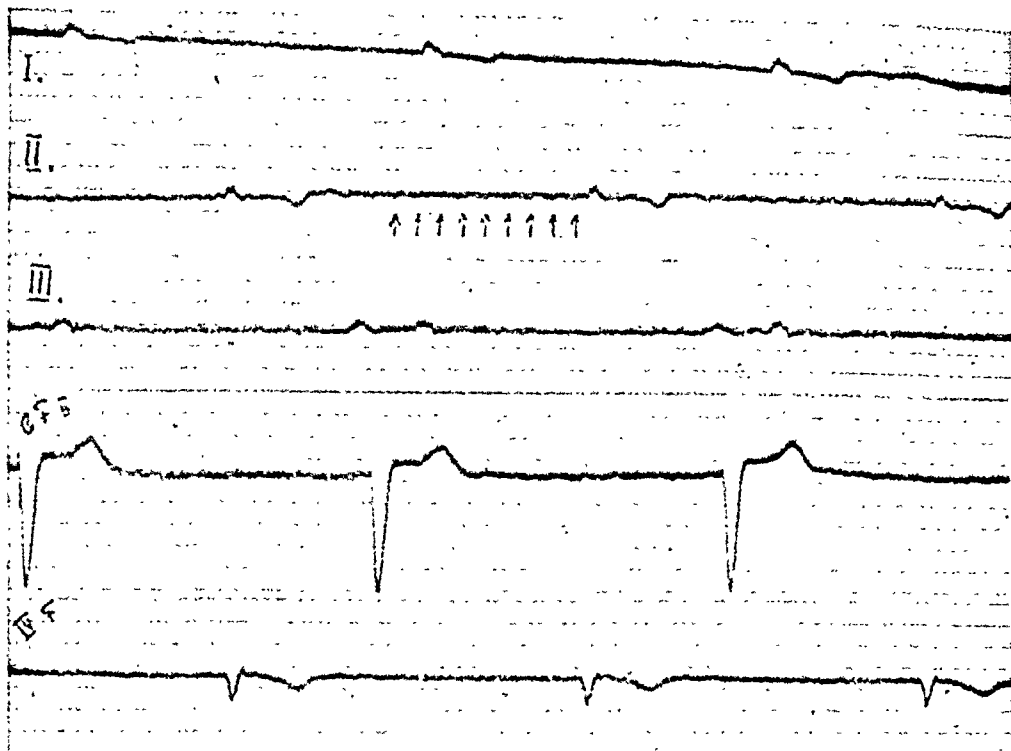


Fig. 2. Case 2, 6/9—40. Auricular flutter and complete auriculo-ventricular block.

pulse deficiency. No pulmonary stasis, enlargement of liver, ascites, or edema. Albuminuria and pyuria present. W. R.: 0. *Elektrocardiogram*: 15/12—36. Auricular fibrillation with rather coarse F-waves. Ventricular action somewhat irregular, c. 80. Initial complexes wide (0.12) and slurred. The greatest deflection positive in Lead I, negative of the S-type in Leads II and III, S—T segments normal.  $T_1$  isoelectric  $T_2$  and  $T_3$  positive. — Managed quite well out of bed and without treatment till 28/8—40. Then complained of a pain in the precordium and a sensation of oppression. No rise in temperature. The day after the action of the heart was 36, regular. 4/9 orthopnoea. Colour pale, cyanotic. Heart sounds very faint, action 28. No basal crepitation, enlargement of liver or ascites. Slight pretibial edema. Blood pressure 150/80. *Electrocardiogram* 6/9—40 (Fig. 2.): Regular F-waves with a frequency of 428 observed most distinctly in Lead II. Ventricular action regular, 27, without fixed relation to F-waves. Initial complexes wide (0.14), low ( $< 0.5$ ), upward directed in all extremity leads.  $T_1$  negative,  $T_2$  positive. Negative initial deflection in  $CF_2$  and  $IV_F$ . S—T elevated in  $CF_2$ , T positive in  $CF_2$ , negative in  $IV_F$ . Later electrocardiograms all showed complete A—V block and auricular flutter (on one occasion, however, auricular fibrillation, it being impossible even with the use of precordial leads both with plate and needle electrodes to demonstrate

regular F-waves). On the other hand, there was a change in the ventricular complexes which in the first pictures had shown changes as in anterior wall infarction, especially in  $CF_2$  and  $IV_F$ , but now assumed an appearance as in branch block of Bayley's type with a deep, broad  $S_1$  and M-shaped  $QRS_{CF_2}$ . The ventricular action was about 36. Treated with aminophyllin and diuregan, but fell gradually into a decline. Died 5 months after the demonstration of auricular flutter and complete A—V block. The postmortem findings were total pericardial symphysis with considerable calcareous deposits, corresponding to the anterior wall of the right ventricle. Hypertrophy and dilatation of the heart. Moderately severe atherosclerosis of the aorta and coronary arteries. Microscopic examination of the myocardium revealed nothing abnormal.

*Epicrisis:* A male patient aged 84 is admitted for an arteriosclerotic affection of the heart with auricular fibrillation and insufficiency symptoms. Barely 4 years later auricular flutter and complete A—V block are found in connection with symptoms of coronary insufficiency. Death supervenes 5 months later.

*Case 3 (J. 720/41).* — Woman aged 65. Admitted 7/3—40, died 28/6—41. Has not had diphtheria, scarlatina, or rheumatic fever. The heart affection set in about 10 years earlier with functional dyspnoea. Committed to hospital for heart disease in 1936. Since 1939 increasing functional dyspnoea, cough, expectoration, tendency to edema, and attacks of angina pectoris. In hospital 10/1—8/2 1940 and thence moved to another hospital where the diagnosis was myocardial degeneration, heart block, angina pectoris, arterial hypertension. *Electrocardiogram* 6/3—40: P—Q 0.28. Action regular apart from a few extrasystoles. Leftsided preponderance. Not treated with digitalis. Moved to 'De gamles By' 7/3—40. Upon admission there were signs of a slight insufficiency. Cyanosis of cheeks and lips but no dyspnoea at rest. Peripheral arteries sclerotic. Pulse 40, regular. Blood pressure 195/100. Heart: Ictus in 6th intercostal space 2 fingers' breadths outside the medioclavicular line, very heaving. Over the whole precordium, most marked at the aorta, is heard a long systolic murmur somewhat rough over the aorta, more blowing at the apex. Action similar to pulse. Pulmonary stethoscopy: râles over both posterior surfaces. No enlargement of liver, ascites, edema, or albuminuria. W. R.: 0. *Electrocardiogram* 9/3—40: Instead of P-waves are seen irregular F-waves, mostly of the fibrillo-flutter type. Ventricular action regular, 40. Initial complexes wide, slurred. Greatest deflection positive in all leads from the extremities. Deep  $Q_2$ . S—T segments normal.  $T_1$  negative.  $T_2$  iso-electric,  $T_3$  slightly positive. In  $CF_2$  the initial complex is diphasic with low, wide, split R-wave, in  $IV_F$  it is quite negative. S—T elevated in  $IV_F$ . — In order to settle whether there was flutter or fibrillation precordial leads were taken with needle electrodes in the 2nd and 5th intercostal space to the right of the sternum (Fig. 3), and distinct uniform F-waves were seen with a frequency

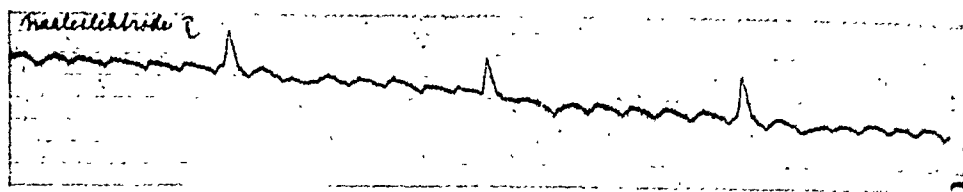


Fig. 3. Case 3. Precordial lead with needle electrodes in the 2nd and 5th intercostal spaces to the right of the sternum. — Auricular flutter and complete auriculo-ventricular block.

of 300. Initial complexes without any fixed relation to the F-waves. Not treated with digitalis or quinidine. Pulse 40—50; some days, however, around 60, and on one occasion 72. The electrocardiogram showed in the main unchanged conditions. Died 15 months after the finding of auricular flutter and complete A—V-block with symptoms of bronchopneumonia. — Autopsy showed severe aortic stenosis with rigid, deformed, conercent valves. Also heavy calcification of the annulus fibrosus of the mitral valve with some mitral stenosis. Considerable left sided hypertrophy but otherwise no macroscopic changes of the myocardium. Some atherosclerosis of the aorta and the coronary arteries.

*Epicrisis:* A woman aged 65, who has had heart symptoms for about ten years is admitted with insufficiency symptoms. Partial A—V block is found and a few days later spontaneous auricular flutter with complete A—V block. She dies 15 months later.

*Case 4* (J. 126/40180). — Man aged 73. Admitted 24/4—42. Previously in good health; has not had diphtheria, scarlatina, or rheumatic fever. For about 5 years functional dyspnoea and a tendency to edema. Committed to hospital in December 1941. The diagnosis here was arterial hypertension, heart insufficiency. Blood pressure 235/110. *Electrocardiogram:* Right bundle-branch block. Not treated with digitalis. Admitted to «De Gamles By» 24/4—42 with symptoms of severe heart disease. There is cyanosis and resting dyspnoea. Peripheral arteries sclerotic. Pulse regular, 44. Blood pressure 240/110. Heart: Ictus felt in the 5th intercostal space outside the medioclavicular line. There is faint fremitus. At apex a long presystolic-systolic murmur.  $A_2$  accentuated. Some pulmonary stasis (X-ray). No enlargement of liver, ascites, or edema. There is albuminuria. W. R.: 0. X-ray: Heart much enlarged both on the right and the left (diameter 20.5 cm, width of thorax 29.55 cm.). The curve of the aortic arch long and prominent. *Electrocardiogram* 27/4—42 (Fig. 4): No P-waves. Ventricular action regular, 36. Initial complexes wide (0.16).  $QRS_1$  diphasic with wide and deep S-wave.  $QRS_2$  negative W-shaped.  $QRS_3$  diphasic with deep  $Q_3$ . S— $T_1$  somewhat lowered. S— $T_2$  normal. S— $T_3$  somewhat lowered.  $T_1$  diphasic,  $T_2$  isoelectric,  $T_3$  somewhat negative. Leads with 2



Fig. 4. Case 4, 27/4—42. Auricular fibrillation and complete auriculo-ventricular block.

electrodes from the precordium showed no P-waves. Treated with aminophyllin, mersalyl, and digitalis without any effect. Is gradually sinking, but still alive. Electrocardiogram on 26/1—43 shows unchanged conditions.

*Epicrisis:* In a man, aged 73, with hypertensive and arteriosclerotic heart disease of about 5 years' standing is found spontaneous auricular fibrillation and complete A—V block. Treatment with digitalis without effect.

*Case 5.* (J. 243/43). — Man aged 76. Admitted 3/13—41, died 1/3—43. Had diphtheria in youth, but otherwise mostly in good health. About 6 months before admission showed a tendency to edema. No other cardiac complaints. On 27/10—41 committed to hospital on account of increasing senile dementia. Moved to «De Gamles By» 3/12—41. Not treated with digitalis. — *Electrocardiogram.* 28/10—41: No P-waves. Ventricular action regular, 39. Initial complexes wide (0.15), split, upward directed in Lead I, downward directed in Leads II and III.  $T_1$  negative,  $T_2$  and  $T_3$  positive. S— $T_1$  somewhat lowered, S— $T_3$  somewhat elevated. — Upon admission no dyspnoea or cyanosis. Peripheral arteries highly sclerotic. Blood pressure 220/110. Heart covered by lung. Ictus not felt. Over the whole precordium a systolic murmur.  $A_2$  accentuated. No pulmonary stasis, enlargement of liver, ascites, edema, or albuminuria: W. R.: 0. *Electrocardiogram* 6/12—41 (Fig. 5): No P-waves. Ventricular action regular, 43. Initial complexes in Lead I wide (0.14), low, split, upward directed; in Leads II and III broad, split, downward directed  $T_1$  isoelectric  $T_2$  and  $T_3$  positive. S— $T_2$  and  $T_3$  isoelectric. — Fairly quickly insufficiency symptoms developed, and the patient died 13 months after admission. Autopsy showed moderate atherosclerosis of the aorta and coronary arteries. The myocardium diffusely hypertrophic with scattered fibroses; no myomalacia. The auricles large and lax. Aortic valves sclerotic. In addition, there was organic stasis and

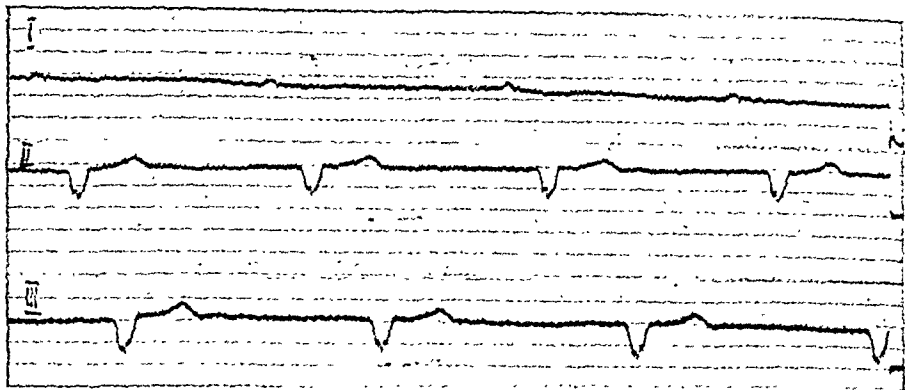


Fig. 5. Case 5, 6/12—41. Auricular fibrillation and complete auriculo-ventricular block.

in the lungs disseminated lobular pneumonias, as well as thrombosis of the branches of the right pulmonary artery.

**Epicrisis.** In a man aged 76 with hypertensive and arteriosclerotic heart affection was found auricular fibrillation and complete auriculo-ventricular block.

**Case 6.** (J. 424/42). — Woman aged 73. Admitted 17/4—41, died 23/4—42. Previously in good health. Heart affection set in about 5 years before admission, with functional dyspnoea and attacks of angina pectoris. Committed to hospital 13/5—41 where the diagnosis was heart disease, aortic arteriosclerosis. *Electrocardiogram:* Auricular fibrillation. Treatment: Digitalis, nitroglycerine. Moved to «De Gamles By» 17/7—41. — On admission no cyanosis or resting dyspnoea. Pulse 52, irregular. Blood pressure 150/80. Peripheral arteries sclerotic. Heart: Ictus felt in 5th intercostal space 1—2 cm outside the medioclavicular line. Systolic murmur over apex.  $P_2$  accentuated. No pulmonary stasis, enlargement of liver, ascites, edema, or albuminuria. W. R.: 0. *Electrocardiogram* 21/7—41: Auricular fibrillation with irregular ventricular action of about 80. — On account of a tendency to edema and accelerated ventricular action (around 120)  $3 \times 10$  cg folii digitalis were administered from 29/3 to 6/9. Discontinued on account of vomiting with simultaneous remoteness and dullness. *Electrocardiogram* 10/9—41: Auricular fibrillation. Ventricular action regular, 38. After digitalis was discontinued the complete A—V block disappeared again. *Electrocardiogram* 16/2—42 showed auricular fibrillation with irregular ventricular action of c. 90 (precordial lead  $CF_2$  and  $IV_F$  showed nothing of special interest, particularly nothing indicating infarction). Gradually declined and died 9 months after admission. — Autopsy showed a hypertrophic heart. In the anterior wall of the left ventricle there was a large myofibrosis. Locally severe atherosclerosis of the coronary arteries.

*Epicrisis:* In a woman aged 75 treated with digitalis on account of auricular fibrillation and insufficiency symptoms a complete A—V block sets in but disappears again after digitalis has been discontinued. Autopsy showed a fibrous anterior wall infarction which had not been diagnosed.

*Case 7.* (J. 1077/330). — Male, aged 77. Admitted 17/10—41. No previous history of diphtheria, scarlatina, or rheumatic fever. Chronic alcoholic. In 1929 committed to the Neurological Department for «neuritis» of the legs. Never subjective heart symptoms. Present admission for social reasons. — No resting dyspnoea or cyanosis. Peripheral arteries somewhat sclerotic. Blood pressure 145/95. Stethoscopy of heart: Ictus in 4th intercostal space in the medioclavicular line. Sounds pure. Action regular. No pulmonary stasis, enlargement of liver, ascites, edema, or albuminuria. No signs of avitaminosis. W. R.: 0. *Electrocardiogram* 23/10—41: In Leads II and III regular P-waves with a frequency of 180. Only every third wave followed by a ventricular complex (P—Q 0.10). Initial complexes low ( $< 0.5$ ), wide, split, diphasic in Lead I, M-shaped in Leads II and III. Action 60. — There was therefore partial A—V block (3: 1) and arborization block. — The patient managed well without treatment until January 1943 when acute insufficiency supervened, with cyanosis, resting dyspnoea, cough, and expectoration; pulmonary stasis, enlargement of liver, and edema. Blood pressure 190/110. *Electrocardiogram* 19/1—43 (after administration of 40 cg folii digitalis): Auricular fibrillation with slow, somewhat irregular ventricular action (c. 48). Also numerous ventricular heterotopic extrasystoles. The ventricular complexes otherwise mainly as before. — Administration of 180 cg. folii digitalis for 5 days, then 10 cg. 5 times weekly, and also mersalyl. *Electrocardiogram* 26/1—43: Auricular fibrillation with slow, practically regular ventricular action. The ventricular frequency varies from 24 to 28. Initial complexes as before. In addition there is a ventricular bigeminy, every ventricular complex being succeeded by a ventricular extrasystole of differing origin and coupling. — After discontinuance of the digitalis the complete A—V block disappeared and an *electrocardiogram* obtained 15/3—43 showed the same conditions as on 19/1—43. — The patient is still in hospital.

*Epicrisis.* An alcoholic aged 77 in whom partial A—V block has previously been found is treated with digitalis on account of acute insufficiency and auricular fibrillation. Following this complete A—V block develops. After discontinuance of the digitalis the complete block disappears, whereas auricular fibrillation persists.

### Discussion.

Frequency. — As already mentioned, auricular flutter with complete A—V block is a rare finding; but the observation in this

department of 3 cases in 4 years would seem to indicate a somewhat more frequent occurrence than suggested by the literature, even though it is taken into account that our material is selected, no patients under 60 being admitted.

**Etiology.** — All our patients suffered from arteriosclerosis, 1 (Case 2) perhaps also from rheumatic infection, and this agrees with earlier observations. In 2 of our cases (6 and 7) the block was due to digitalis and disappeared after discontinuance of the drug.

With auricular flutter and fibrillation there is, as is well known practically always so-called functional block. This is due to the fact that some of the very numerous auricular impulses reach the auriculo-ventricular node in its refractory period and therefore are not transmitted. There is no actual reduction of the capacity of conduction. If, on the other hand, this is the case owing to toxic or organic injury to the conductive tissue there is a possibility that complete block may occur. The most frequent toxic action on the conductive tissue is due to digitalis which may cause all degrees of block. The effect is partly due to the fact that the refractory period is prolonged, partly to the circumstance that the excitability is reduced.

**Classification.** — On the basis of the literature and the author's own cases it seems natural to classify the cases of auricular flutter or fibrillation with complete A—V block in two main groups: 1. The spontaneous cases. 2. Those caused by medication. Each of these groups may then perhaps be subdivided into a) the cases with complete block where there is previous flutter or fibrillation and b) the cases where flutter or fibrillation sets in when there is previously complete block. As will appear later, this grouping may be of importance for the treatment.

**Diagnosis.** — Clinically the diagnosis can only be made with tolerable certainty in the cases where a patient with auricular fibrillation or flutter suddenly develops bradycardia with regular heart action under 50. Further, auricular flutter with complete block may be surmised if pronounced bradycardia is found, with regular pulsation of the jugular during diastole. This, however, will be of more theoretical than practical interest. Only by electrocardiography can a conclusive diagnosis be obtained.

Bradycardia is no cardinal symptom of complete A—V block.

A frequency of over 60 is common, and cases with an action of over 100 (Scherf) have been observed. The frequency depends on the situation of the idioventricular impulse centre. The higher it lies, the better developed is its automatism. In high-lying block with idioventricular impulse centre situated just distally to the block the rhythm is only 15—20 beats slower than the sinus rhythm (Scherf), unless the same phenomenon which has caused the block has also injured the deeper-lying centres.

In auricular flutter with complete A—V block the electrocardiogram shows in one or more leads, as a rule most plainly in leads II or III, regular F-waves with a frequency mostly ranging between 200 and 350. If the F-waves are not distinct it may sometimes be useful to take precordial leads. Leading off is then best done with 2 electrodes from the 2nd and 5th intercostal space respectively, just to the right of the sternum. The electrodes may be circular plate electrodes as is usual with precordial leads, or needle electrodes introduced into the subcutaneous tissue. In our Case 3, no distinct F-waves were seen in the leads from the extremities, while on the other hand they were distinct and regular in the precordial lead, thus showing an apparent fibrillation to be a flutter. The line of demarcation between flutter and fibrillation must on the whole be said not to be sharp (cf. the term fibrillo-flutter), as indeed our Case 2 indicates. Here it was not possible to demonstrate regular F-waves in all the cardiograms, so that it is a matter of opinion whether one prefers to regard it as a flutter or a fibrillation.

The ventricular complexes appear with a regular rhythm and without any fixed relation to the F-waves, in contrast with auricular flutter with a high degree of incomplete A—V block (5: 1, 6: 1), where there is a fixed relation between the ventricular complexes and the preceding F-wave. As an example of 5: 1 A—V block simulating complete A—V block may be mentioned the following case:

A woman, aged 60 (J. 1206/57920). Admitted 6/12—39. As a child she had chorea and three times rheumatic fever. When about 50 years old she was three times treated in hospital for «rheumatism». 54 years old hospitalised for a heart affection. On 15/5—39 admitted to the psychiatric department for depression, incipient senile dementia. Moved to «De Gamles By». — Upon admission presented symptoms of moderately severe heart disease. There was some dyspnoea and cyanosis. Pulse about 70, somewhat arrhythmic. Peripheral arteries rigid. Blood pressure 170/110. Stethoscopy of





automatic impulse issues from a centre which lies directly below the block and above the bifurcation of the auriculo-ventricular bundle. If, on the other hand, it lies distally to the bifurcation the complexes will be wide and assume the appearance of ventricular extrasystoles and of intraventricular block. This is due to abnormal spreading and need not therefore be caused by myocardial injury. If, again, the ventricular complexes are changed after complete block is established as in several of our cases, it must be supposed to be due to myocardial damage.

Therapy. — Gager recommends treatment of the spontaneous cases in which the block has succeeded a pre-existing auricular flutter with quinidine or digitalis, or perhaps both, in the hope of establishing sinus rhythm. If this proves successful there is a possibility that the complete block also will vanish, namely if it has in great part been functional. He himself describes a case in which this happened after treatment with quinidine, while digitalis was without effect. Partial block, however, remained. Jourdonais and Mosenthal obtained the same result, but in their patient the partial block was changed into a complete block while sinus rhythm persisted.

Kerr and Bender point out one of the dangers of quinidine treatment. One of their patients with auricular fibrillation and complete A—V block developed ventricular fibrillation during quinidine treatment.

According to Wenckebach and Winterberg it is of no great clinical significance for the function of the heart that auricular flutter or fibrillation is complicated with a complete A—V block, and the treatment should therefore be on the same lines as in uncomplicated cases. Our patients have been treated on this principle.

Perhaps it should be pointed out that the administration of digitalis to these patients is by no means counterindicated unless the complete block is due precisely to digitalis. In that case it will vanish when digitalis has been discontinued for some time.

### Summary.

After reference to previously described cases of auricular flutter with complete A—V block three new cases are described, as also 4 cases of auricular fibrillation with complete A—V block.

The material comprises 4 men and 3 women, of ages ranging from 65 to 84 years. The etiology of the heart affection was in all cases coronary sclerosis or hypertension and in a single case perhaps also a rheumatic affection. In 2 cases the complete A—V block was due to digitalis; the remaining cases were spontaneous. The time of survival was from 5—26 months; 2 patients are still alive.

The cases are as a rule diagnosed by electrocardiography. There is not always bradycardia. The employment of leads with 2 electrodes from the precordium is mentioned. It is pointed out that there is no sharp line of demarcation between auricular flutter and auricular fibrillation. Mention is made of the differential diagnosis of auricular flutter with a high degree of A—V block.

The appearance of the initial complexes is discussed. An abnormal shape need not be due to a myocardial damage.

Finally the therapy is discussed.

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## The effect of adenosintriphosphate and B<sub>1</sub> vitamin in degenerative spinal cord diseases.

A Clinic-therapeutical Study.

By

T. de LEHOCZKY.

(Submitted for publication March 29, 1943).

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It is an established fact that the nerve tissues can function only if amply supplied with carbohydrate, the reason for this being that carbohydrate metabolism is the chief source of energy of the nerve substance. An indirect proof of this is that unconsciousness brought on by hypoglycemia can be overcome immediately by the use of carbohydrates (Huszk).

The importance of the metabolism of carbohydrate is closely connected with B<sub>1</sub> vitamin research, especially since the discovery that the carbohydrates are consumed in the brain substance on the introduction of pyruvic acid ( $\text{CH}_3 \cdot \text{Co} \cdot \text{COOH}$ ) but only in the presence of B<sub>1</sub> vitamin. Later it was shown that it is not the free form of vitamin B<sub>1</sub> that acts as a catalyst, but the phosphorylated form, cocarboxylase (Lohmann-Schuster, 1937, Westerbrink—Goudsmit 1938, Banga—Ochoa—Peters 1939), and that the living tissue is able to phosphorylate B<sub>1</sub> vitamin (Ochoa—Peters). Banga, Ochoa and Peters proved this with regard to brain tissue (1939). Furthermore it was found that for the intermediary metabolism of carbohydrate C<sub>4</sub> dicarboxylic acids are needed in addition to active B<sub>1</sub> vitamin. (Szent-Györgyi et al. 1937). Such acids are succinate, fumarate and malate.

Thus B<sub>1</sub> vitamin in itself does not affect the metabolism of carbohydrate, since the presence of phosphorus, in particular adenosine-triphosphate, is necessary. On the other hand earlier observations showed that the phosphorylated B<sub>1</sub> vitamin penetrates the tissue only with difficulty and this therefore suggests that «vitamin B<sub>1</sub> permeates the tissue walls as such and is then phosphorylated within the cell» (Banga — Ochoa — Peters 1939).

The above observations make it perfectly clear why pure B vitamin has no favourable influence on the various degenerative nervous disorders (myelopathy, disseminated sclerosis, etc.). For obtain a beneficial effect the B vitamin must be made active or phosphorylated, and this rarely or never occurs in the case of degenerative nervous disease. Earlier successes prescribed to pure B<sub>1</sub> vitamin were probably due to the fact that before, during, or after the B<sub>1</sub> vitamin cure, liver extract was administered to the patients, mostly because of anaemia, and, as Teglbjaerg has shown, liver preparations contain phosphates, various enzymes and even cocarboxylase. Thus the simultaneous administration of these preparations with B<sub>1</sub> vitamin made the phosphorylation of the latter possible.

Finally I should like to mention that Tauber's experiments (1938) show that healthy duodenal juice is also an important factor in the production of cocarboxylase by the organism. Petri and his collaborators proved since 1930, by systematic experimental investigations that gastrectomy was followed by a very severe chronic illness characterized especially by nervous symptoms. So Nørgaard (1939) demonstrated severe pathologic alterations in all parts of the nervous system of total gastrectomized young pigs. — Furthermore Sinclair was able to demonstrate destruction of the vitamin when incubated in vitro with gastric or duodenal juice from patients with achlorhydria. Teglbjaerg (1939) proved the great importance of the healthy gastro-duodenal system by effecting cures in cases of severe pellagra and peripheral neuropathy with stomachic mucus-membrane extracts. Such preparations are: stomopson, mucotrat, ventraemon (Organon), ventrepar (Egger), perstomin (Richter), etc.

It is possible that the use of the stomachic extracts introduces such substances into the organism as facilitate the transport form of vitamin B<sub>1</sub>, which on the ground of Goodhart-Sinclair (1939)

experiments may take place in combination with protein, — or such enzymes which enable the organism to use the phosphorus compounds for phosphorylation.

It is obvious that the regular metabolism of carbohydrate depends on the presence and efficacy of various enzymes, and now Ochoa's (1939) experiments seem to suggest that magnesium or manganese ions must be present in the enzyme system.

In the following, I shall give an account of some therapeutic experiments where two substances, B<sub>1</sub> vitamin and adenosinetriphosphate were indispensable to the metabolism of the carbohydrate in the nerve substance.

Of the 20 cases treated 7 were cases of myelopathy, 12 multiple sclerosis (disseminated sclerosis) and one disseminated encephalomyelitis.

Treatment in every case consisted of 20—25 injections of B<sub>1</sub> vitamin (10 mg vitaplex B<sub>1</sub>, Chinoin) and the same number of adenosinetriphosphate injections (Atriphos, Magyar Gyógyszer Co. Ltd.) administered simultaneously. For the first 8—10 days the injections were given daily and afterwards every second day. During the treatment, of course, no other medicine was given so that the effect might be obtained uninfluenced by other factors.

### Myelopathy.

In the myelopathic (previously: myelosis) group I have included all degenerative spinal diseases which are restricted to the spinal white substance and which are not caused by inflammation. Following the precedent of Davison-Keschner I have divided them into three sub-groups: 1. genuine or toxic, 2. vascular or circulatory, 3. compressive myelopathy. (See T. Lehoczky: *Budapesti Orvosi Ujság* 1942 45, 46, and *Fortschritte der Neurologie* 1942. XIV. page 385).

Of the seven cases in this group six were genuine or toxic, and one was a case of compression.

1. Female, 53 years, fairly severe spastic-atactic paraparesis, slight segmental hypaesthesia. After treatment: great improvement in gait both subjectively and objectively, hardly any ataxy, disappearance of right side Babinski sign, great improvement in left leg

paresis. Slight Barré-sign; which on admission was strongly positive, left leg could be raised  $90^\circ$  as opposed to  $30^\circ$  before.

2. Male, 49 years, fairly severe spastic paraparesis. After treatment moderate improvement in gait objectively and subjectively, patient able to raise legs and move toes on left foot, and to lift right leg to an angle of  $90$  degrees, all of which were previously impossible.

3. Male, 42 years, mild spastic paraparesis. After treatment no traces of spasticity or right side Babinski sign, patient subjectively stronger.

4. Male, 42 years, very severe spastic paraplegia, hypaesthesia from L 1 downwards. After treatment patient subjectively stronger, and able to move toes freely, which before treatment was impossible.

5. Male, 33 years, moderate atactic form, latent paresis. After treatment great improvement in ataxy, right side latent paresis disappeared (Barré sign negative).

6. Female, 42 years, severe spastic paraplegia. After treatment patient was able to move feet, which before had been quite impossible.

7. Female, 74 years, moderate spastic atactic form: distal hypaesthesia affecting all four limbs. Condition unchanged after treatment.

It can be seen that in 6 cases considerable improvement was obtained in ataxy, in the degree of paresis, while in two cases (1 & 3) cessation of the Babinski signs occurred. All patients felt stronger and there was an improved all-round feeling. The failure of the seventh case to respond to treatment was due to the fact that it was a case not of genuine but of compressive myelopathy. After seeing that no effect was obtained by the treatment I gave an lipiodol injection, which showed arrest at the level of the 3rd cervical vertebra. Of course, we cannot effect a cure in cases of myelopathy due to such origin.

### Multiple sclerosis (disseminated sclerosis.)

First I should like to point out that the etiology of multiple sclerosis is still uncertain. As opposed to the earlier supporters of the infection theory, modern researchers, among them van Bogaert, Pette, attribute greater importance to neuro-allergy. In my opi-

nion this is immaterial in studying the therapeutic effect, as it does not affect the course of the cure, and also the essential of the disease in both the clinical and anatomical pictures is *the degenerative component*, which causes focal degeneration in the path system of the spinal white substance.

### 1. *Mild group: 4 cases.*

Characteristic of all cases in this group was the subjective feeling of tiredness, while individually, the subjective signs were girdle sensation and unsteady gait. The objective observations showed: ataxy, nystagmus, pathological reflexes, mild paresis, diplopia, temporal decoloration of the disc, etc. After treatment every patient felt stronger and the sense of tiredness had diminished. Objectively the improvement was shown by a considerable decrease in ataxy in every case, with cessation of paraesthesia, diplopia, intention tremor and of Achilles clonus in the individual cases.

### 2. *Fairly severe group: 5 cases.*

Condition before treatment: high degree of ataxy, more or less developed spastic paraparesis, pathological reflexes, etc. After treatment: two patients showed considerable improvement. In one of these ataxy and right side Babinski sign completely disappeared, while in the other the spastic component of the gait vanished (patient no longer tensed legs and shuffled when walking), the left side Barré-sign was negative, and the latent paresis vanished too. In the other cases the patients showed a decrease in the degree of ataxy, gait was more steady, and in one case I noticed cessation of right side facial paresis.

### 3. *Two severe and one very severe case.*

In the former two cases a slight improvement in the locomotor ataxy was noticed, and in one of them a subjective decrease in the spasticity. In the very severe case (spastic quadruplegia) we observed a decrease in the hand clonus which had caused the patient much suffering, and a subjective and objective increase in strength of the patient. On admittance patient had been unable to stand without support, but after treatment could do so.



Finally a few words about the one case of disseminated encephalomyelitis. Patient was a young girl of 18 years of age, and the illness was in the third year of its course. I included this patient in my experiments, because, the patient had, after the close of an unusually violent and spreading course of the disease, lapsed into a more or less stationary condition showing all the symptoms of multiple sclerosis: — nystagmus, intention tremor, marked locomotor ataxy, spastic paraparesis, pathological reflexes (positive Babinski, — Oppenheim signs etc.) It is obvious that we are now dealing with the course of a degenerative spinal disease which was probably the continuation of an originally violent acute multiple sclerosis. It is well known that in a certain number of cases the borderline between the two diseases is uncertain. After treatment the subjective tiredness and the hand paraesthesia had diminished, objectively it was observed that among the pathological reflexes the left side Oppenheim sign ceased, and the head tremor was reduced.

Thus in the multiple sclerosis group all the patients reported themselves subjectively considerably stronger, and an improvement in gait and paraesthesia. This was borne out by objective observation with a more or less marked improvement in ataxy. In subgroups 2 & 3 there was a lessening in the spasticity, a decrease in some cases of the organic neurological signs (cessation of Achilles and hand clonus, diplopia, intention tremor, right side Babinski and left side Oppenheim signs in one or other of the cases).

An important point is that 1—1 ½ years ago, I treated five of the patients (one mild case, 3 fairly severe and 1 severe) with nicotinic acid (Vitaplex N, Ch.), and after a certain time when the relapse occurred, I started the present system of treatment, obtaining thereby in general the same degree of success as was obtained in the earlier treatment with nicotinic acid. Remembering that the disease is degenerative and progressive this fact in itself is an outstanding therapeutic success. Moreover, one of the patients suffering from ataxy who was unaffected by the nicotinic acid treatment, has shown considerable improvement after the present treatment, while a second patient with spastic muscle tension after failure to respond to nicotinic acid now shows some improvement.

### Summary.

After having administered B<sub>1</sub> vitamin and adenosinetriphosphate together, I observed that great improvement was obtained in two groups of degenerative diseases of the spinal cord: myelopathia and multiple sclerosis. The improvement was not only subjective patients felt stronger, gait was more steady, decrease in paraesthesia — but it also showed itself in the objective neurological signs (ataxy, paresis, tremor), and even in the cessation of certain organic signs: for example in 3 cases the Babinski signs, in three cases the Barré signs and in one case the Oppenheim sign ceased.

The reliability of my results is increased by the fact that the patients were under treatment for only a relatively short time, in an average 4 weeks, thus in judging the results the possibility of spontaneous remissions can practically be left out of account. A complete survey of the results of the treatment can be given only after more protracted and possibly repeated treatment, but on the basis of the present results it is clear that B<sub>1</sub> vitamin and adenosinetriphosphate, two chemical substances indispensable to the carbohydrate metabolism in the nerve tissue, produce, when administered together, in cases of degenerative diseases of the spinal white substance, a marked improvement both subjective, and objective.

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## Rheumatic Invalids in Sweden.

A Socio-Medical Study.

By

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(Submitted for publication May 3, 1943.)

State pensions granted for reasons of permanent incapacity for work due to chronic articular rheumatism are enjoyed by a large number of persons in Sweden. At the present time it is not possible to obtain exact information as to the number of these invalids, but an approximate figure can be arrived at by means of certain calculations.

In the year 1918 about 7.2 % of the accession of male pensioners and 10.3 % of the accession of female pensioners consisted of persons who had been pensioned as a result of incapacity for work due to rheumatic affections.<sup>1</sup> In 1928 the corresponding percentages were 11.3 and 13.3 % respectively.<sup>2</sup> If it is assumed that both these investigations were carried out on identical principles, and further that the proportion of rheumatics among the pensioners increased fairly evenly from year to year, these figures can be employed for calculating the annual accession of pensioned rheumatics by applying these percentage figures to the available figures for the number of fresh accessory pensions for the years 1918—1936. In this way we can probably calculate the number of pensioned rheumatics

<sup>1</sup> Kahlmeter, Acta Medica Scand. LIX, 1923.

<sup>2</sup> 1928 Pensions Insurance Committee: Government Off. Investigation 1930:15.

during the years 1918—1936 at approximately 46,000 men and 63,000 women. If it is assumed that the average age of all the men pensioned for different reasons was 62—64 years at the time they were pensioned, and that of the women 61—63, an approximate calculation can then be made of the survivors at the end of 1942, presupposing a normal mortality within the population. The number of survivors will be 31,000 men and 42,000 women, which implies that there are at the present time fully 70,000 pensioned rheumatics in the country. If we calculate with a mortality of twice the normal, which is hardly reasonable, we arrive at about 40,000 survivors.

Thus, the percentages given above for the accession of rheumatic pensioners during the years 1918 and 1928 — 7.2 and 10.3 % and 11.3 and 13.3 % respectively — might possibly indicate that the number of rheumatics among the pensioners increases year by year relatively to other pensioners. It is possible, but by no means certain, that this is the case. The difference between the figures may be conditioned, firstly, by the fact that the two investigations were conducted by different investigators, who had different possibilities of sifting the material diagnostically, and secondly — and particularly — by the fact that the 1928 investigation referred to material which was considerably larger and — thanks to the development of nursing activities — »purer» than the 1918 material. It will therefore probably be most correct for the present to assume that, on the whole, the proportion of rheumatics among the accession of pensioners has remained constant since the 1928 investigation. If this is the case, the number of pensioned rheumatics will naturally be somewhat lower, viz. 41,000 men and 59,000 women. With normal mortality the number surviving would then be c. 65,000, and with double the normal mortality c. 32,000 persons.

If it is now assumed (which is not demonstrated, but quite plausible) that the mortality figure for rheumatic invalids is higher than for the normal population, we reach the result that at the present time (1942) at least 50,000 persons receive premature pensions on account of rheumatic affections.

That this theoretical figure must tally fairly well with the actual conditions is corroborated by calculations made in another way. In year 1936 a total of 400,000 persons received premature pensions on account of various diseases. If we assume that the proportion

of rheumatics among the pensioners has not changed to any degree worth mentioning since 1918 and 1928, and thus make use of the average percentages for additional rheumatics for these years, which is 10.5 %, we reach the result that the aggregate of persons pensioned in 1936 owing to rheumatic affections was 42,000.

Thus it is probable that, at the present time (1942), between 40,000 and 50,000 persons in Sweden receive premature pensions on the ground of rheumatic affections.

### **The scope and technique of the investigation.**

Both from the social and medical points of view it must be of particular interest to arrive at a conception of the circumstances of the rheumatic invalids in various respects. Are these sufferers well looked after? Is everything possible done for their care? Are they all to be considered definitively disabled, or could some of them be helped to improved health by means of the therapeutic measures which are now available, and thereby be returned to productive work, at least be made to a certain degree self-supporting?

With the object of seeking answers to these questions, I have made an investigation into the circumstances of a proportion of the Swedish rheumatic invalids, which has been possible thanks to the wellordered organization of the State Pensions Insurance.

From the archives of the Pensions Board, where all papers concerning the prematurely pensioned are assembled, 1,100 documents referring to rheumatic invalids were taken at random. Only documents relating to rheumatic invalids who had previously received treatment through the instrumentality of the Pensions Board were available. Those suffering from rheumatism who proved to be already so severely disabled when they applied for pensions that hospital treatment could not reasonably be expected to improve their condition to any extent worth mentioning, were pensioned without first being recommended for treatment. It has not been possible to calculate the number of these latter invalids. It might of course have been of interest to investigate also the circumstances of this category of rheumatic invalids, which possibly comprises the most

severely disabled. This cannot be done, however, without a detailed examination of the documents dealing with all persons pensioned for all possible reasons, which is in practice impossible.

The available investigation material was first carefully examined and worked up. Then a questionnaire concerning the pensioners, formulated as shown below, was sent out to the Chairmen of the Municipal Pensions Boards, who then got into contact with the invalids in question, so that they were able to supplement their previous personal knowledge of them by making themselves acquainted with their condition and circumstances at the time. A record of the answers to the questions was then made, and the questionnaire returned to the investigator. Of the 1,100 questionnaires sent out, considerably over 1,000 were returned conscientiously filled in. The cases which were then worked up were those of the 1,008 whose questionnaires had been returned fully filled in when the investigation was set on foot in June 1942.

All the information collected in this way, both from the Pensions Board and the local Pensions Committees, was then worked up statistically.

The following was the questionnaire sent out:

- 1) Present postal address:
- 2) a) Has the invalid his (her) own dwelling?  
b) Is he (she) living with others?  
c) Has he (she) a separate room or do several live together?  
d) Is the house satisfactory (damp, draughty, dark)?
- 3) a) Is the invalid in a home for chronic invalids?  
b) If so, since when?
- 4) a) Is the invalid lying in bed on account of the articular affection?  
b) If so, since when?
- 5) Can the invalid, in spite of the articular affection:  
a) Manage entirely alone?  
b) Eat without help?  
c) Dress without assistance?  
d) Walk without assistance?
- 6) If the invalid is not in an institution but requires daily help, what help is available?

- 7) a) Can the invalid perform any work?  
 b) Can he (she) keep the room in order?  
 c) Can he (she) prepare his (her) own food?  
 d) Can he (she) do any remunerative work?  
 e) If so, what?
- 8) a) What is his (her) annual income, apart from the pension?  
 b) Municipal relief?
- 9) Does the invalid suffer from any severe illness other than the rheumatism?
- 10) Can the invalid be considered to be well looked after?  
 If this is not the case, in what respect would a change be desirable?

### The working up of the material.

The investigation material thus covers 1,008 persons pensioned owing to chronic articular rheumatism and was taken at random from the archives of the Pensions Board.

By far the greater proportion of the pensioners belong to the groups employed in manual labour.

#### *Distribution by sex.*

384, or 38 %, were men and 624, or 62 % women (table 1). The considerable preponderance of women is due in the first place to the fact that women are more often affected by chronic polyarthritis than men. In an investigation of 975 cases of chronic articular rheumatism from the Royal Pensions Board's material, Kahlmeter<sup>1</sup> (1927) found that 41 % were men and 59 % women. In Denmark Nyfeldt<sup>2</sup> (1942) found that, of those who were attacked by chronic polyarthritis, 75 % were women and 25 % men. Similar figures have been given from English quarters. Dawson<sup>3</sup> states that in U. S. A. chronic progressive »rheumatoid arthritis» is met with three times as often in women as in men. German authors in general appear also to have found a preponderance for women, although a less pronounced one. It is thus clear that chronic polyarthritis more often afflicts women than men.

In the present investigation material are included the cases of deformative arthritis which led to premature pensioning. As this form of chronic articular disease is considered to occur approxima-

<sup>1</sup> Hygiea, Bd 89 (1927).

<sup>2</sup> Ugeskr. Læg. Bd. 94 (1932).

<sup>3</sup> Nelson Loose Leaf Medicine, Bd 5.



tely equally often in men as in women, this naturally has a levelling effect on the percentages for the two sexes. If this is taken into consideration, the percentile distribution by sex in the investigation tallies fairly well with the morbidity figures for the respective sexes. It can therefore be established that men and women are disabled to approximately the same extent when they develop chronic articular rheumatism.

Table 1.

A distribution of the material according to sex, age and civil status.

Age at time of investigation	Civil status					
	single	married	widower or widow	divorced	unknown	Total
Men:						
15—19	2	—	—	—	—	2
20—24	7	—	—	—	—	7
25—29	21	2	—	—	1	24
30—34	25	4	—	—	2	31
35—39	26	21	1	—	1	49
40—44	26	43	1	—	2	72
45—49	30	65	3	3	1	102
50—54	17	68	3	—	4	92
55—59	—	4	—	—	—	4
60—64	—	1	—	—	—	1
Total	154	208	8	3	11	384
%	40.1	54.2	2.1	0.8	2.9	100
Women:						
15—19	4	—	—	—	—	4
20—24	19	—	—	—	2	21
25—29	41	1	—	—	1	43
30—34	49	6	—	—	2	57
35—39	57	24	1	—	3	85
40—44	51	23	8	4	2	88
45—49	62	60	11	4	6	143
50—54	53	89	19	6	10	177
55—59	1	2	—	—	2	5
60—64	—	1	—	—	—	1
Total	337	206	39	14	28	624
%	54.0	33.0	6.2	2.2	4.5	100

*Civil status.*

As regards civil status, it is found (table 1) that, of the men, a somewhat larger number were married than unmarried, and that the opposite was the case for the women, so that there were considerably more unmarried women than married. This circumstance may conceivably be connected with the fact that the unmarried women are compelled to a greater extent than the married ones to seek financial assistance in the form of pensions. If a married woman is disabled, the home can often be kept going with the help of the children and husband. On the other hand if a married man is disabled, the family probably has no possibility of subsistence, and the husband is therefore compelled to apply for a pension.

*Age distribution.*

If the investigation material is scrutinized in respect of age, it is found (table 1) that at the time of the investigation the majority of the men were between 35—54 years of age, and the majority of the women between 25—54. This might indicate that women are affected and disabled by chronic articular rheumatism earlier than men. Only a few are pensioned before the age of 25. This will probably be due partly to the fact that «infection arthritis» is most usual between the ages of 20—40, and partly to the fact that the younger age classes are better taken care of by their families, and that in spite of their incapacity for work, they are provided for by the family in the hope that the illness will be temporary. The low figures after the age of 54 are fully explained by the fact that, as has been explained above, the investigation only comprises the invalids who, once or oftener, had received medical and nursing care through the agency of the Pensions Board, and that generally such medical care, for insurance-technical reasons, is not given to invalids who have reached the age of 55. Thus the sufferers from chronic polyarthritis who became affected at the age of 54 or later, and who were incapacitated and granted pensions, are not included in the investigation material, and it has not been possible to investigate the circumstances of these invalids more closely.

*The degree of disablement,*

For purposes of working up the material, the pensioners have been divided into three groups as regards the degree of disablement. It has been possible to do this, firstly with the help of the doctor's expression of opinion accompanying the application for a pension, and secondly with the support of the careful expression of opinion from the doctor which was issued after the treatment which the pensioner had previously received at the various hospitals of the Pensions Board. In group 1, the least disabled, have been included such cases as only had joints attacked by the disease now and again and relatively low S. R. In group 2, the moderately incapacitated, are included cases in which several joints were attacked. In group 3 have been collected the cases which were extremely disabled, with symptoms from the majority of joints, and usually with a deteriorated general condition.

Table 2.

The degree of disablement at different ages.

Age at time of investiga- tion	Total number = N	of which in disablement degree					
		1		2		3	
		number	% of N	number	% of N	number	% of N
Men:							
0—30	33	10	30.3±8.0	12	36.4±8.4	11	33.3±8.2
30—35	31	5	16.1±6.6	17	54.8±8.9	9	29.0±8.2
35—40	49	6	12.2±4.7	25	51.0±7.1	18	36.7±6.9
40—45	72	8	11.1±3.7	38	52.8±5.9	26	36.1±5.7
45—50	102	16	15.7±3.6	48	47.1±4.9	38	37.3±4.8
50—∞	97	14	14.4±3.6	42	43.3±5.0	41	42.3±5.0
Total	384	59	15.4±1.8	182	47.4±2.5	143	37.2±2.5
Women:							
0—30	68	6	8.8±3.4	26	38.2±5.9	36	52.9±6.1
30—35	57	9	15.8±4.8	18	31.6±6.2	30	52.6±6.6
35—40	85	15	17.6±4.1	33	38.8±5.3	37	43.5±5.4
40—45	88	11	12.5±3.5	40	45.5±5.3	37	42.1±5.3
45—50	143	24	16.8±3.1	42	29.4±3.8	77	53.9±4.2
50—∞	183	26	14.2±2.6	68	37.2±3.6	89	48.6±3.7
Total	624	91	14.6±1.4	227	36.4±1.9	306	49.0±2.0

If a comparison is made of the proportion of the two sexes with a particular degree of disablement, it is found (table 2) that approximately equal numbers come under disablement degree 1, with about 15 % for each sex. On the other hand, degree 2 is more numerous among the men than among the women, with 47.4 and 36.4 % respectively (the difference is  $11.0 \pm 3.0$ ). If the material is analysed more closely with the object of investigating whether any special age-group is responsible for this difference, it is found that this is not the case. Degree 2 is more numerous in men in all the age groups, except in the lowest (30 years). From what has been said, it follows that degree 3 shows inverse conditions if a comparison is made between the sexes. The percentage figures for degree 3 are 37.2 % for men and 49.0 % for women. Thus it would seem as though the severest degree of disablement is more often met with in women than in men. If an explanation of this is sought, the circumstance mentioned above, that in general the disablement begins earlier in women than in men, may be indicated. Consequently the duration of the illness is also longer, and the probability of severer disablement is increased. This circumstance may also be partly explained by the different modes of reaction as between the sexes. Women are more frequent-

Table 3.

Degree of disablement and civil status.

Civil status	Total number = N	of which in degree of disablement					
		1		2		3	
		number	% of N	number	% of N	number	% of N
Men:							
Married ....	208	30	14.4 ± 2.4	95	45.7 ± 3.5	83	39.9 ± 3.4
Unmarried							
Widowers and							
Divorced ....	165	27	16.4 ± 2.9	81	49.1 ± 3.9	57	34.5 ± 3.7
Women:							
Married ....	206	31	15.0 ± 2.6	66	32.0 ± 3.3	109	52.9 ± 3.5
Unmarried							
Widows and							
Divorced ....	390	54	13.8 ± 1.7	148	37.9 ± 2.6	188	48.2 ± 2.5

ly affected by the disease than men, and therefore it is possible that, on an average, women also suffer from severer forms, which lead to a greater degree of disablement.

The degree of disablement does not appear to show any marked connection with the civil status (table 3). On the whole, both the married and the unmarried pensioners are equally distributed over the different degrees of disablement.

A survey of the material on the basis of the age at the time of the last treatment, in combination with the degree of disablement (table 4) shows that, on the whole, the distribution within the different degrees of disablement is similar within the different age groups. An inconsiderable tendency towards an increase in the average age can be discerned, however, in both men and women. Thus in the degree of disablement 1 the average age of men at the time of the last treatment was 37 years, and in degree 3 it was 39.5 years. In the case of women the corresponding age figures are 38 and 39 years.

Table 4.

Age at last period of treatment in the different degrees of disablement.

	degree of disablement			
	1	2	3	1—3
Men:				
lower quartile .....	27.0	31.3	32.7	31.8
median quartile .....	37.2	38.3	39.5	38.5
upper quartile .....	43.0	43.6	44.6	43.8
Women:				
lower quartile .....	31.1	30.1	29.5	30.2
median quartile .....	38.3	37.7	39.0	38.5
upper quartile .....	43.5	42.7	44.0	43.4

It is of interest to examine whether the degree of disablement shows any connection with the interval which had elapsed between the date of the last institutional treatment reported and the date of the investigation (table 5).

If, to begin with, the whole material (younger + older) is examined, the figures for both men and women show that in general

Table 5.

The distribution of the material over the degrees of disablement in combination with the interval between the last period of treatment and the investigation.

Interval between the last period of treatment and the investigation, years	Total number = N	of which in degree of disablement					
		1		2		3	
		number	% of N	number	% of N	number	% of N
Men:							
younger:							
2—6	103	18	17.5±3.7	46	44.7±4.9	39	37.9±4.8
7—∞	82	11	13.4±3.8	46	56.1±5.5	25	30.5±5.1
elder:							
2—6	114	11	9.6±2.8	51	44.7±4.7	52	45.6±4.7
7—∞	84	19	22.6±4.6	38	45.2±5.4	27	32.1±5.1
younger + older:							
2—6	217	29	13.4±2.3	97	44.7±3.4	91	41.9±3.3
7—∞	166	30	18.1±3.0	84	50.6±3.9	52	31.3±3.6
Women:							
younger:							
2—6	167	24	14.4±2.7	60	35.9±3.7	83	49.7±3.9
7—∞	131	17	13.0±2.9	57	43.5±4.3	57	43.5±4.3
older:							
2—6	167	24	14.4±2.7	39	23.4±3.3	104	62.3±3.8
7—∞	158	24	15.2±2.9	71	44.9±4.0	63	39.9±3.9
younger + older:							
2—6	334	48	14.4±1.9	99	29.6±2.5	187	56.0±2.7
7—∞	289	41	14.2±2.1	128	44.3±2.9	120	41.5±2.9

the shorter the time between the last treatment and the investigation the more severe was the disablement. This appears particularly clearly in the case of women. Among those who had been last treated 6 years before, at the most 56.0 % exhibit degree 3, as against 41.5 % among those who had been in receipt of treatment a longer time before (at least 7 years). The difference is  $14.5 \pm 4$  —

Table 6.

The interval (years) between the last period of treatment and the date of pensioning.

	degree of disablement			
	1	2	3	1—3
Men:				
lower quartile .....	1.1	0.6	0.5	0.6
median quartile .....	2.2	1.3	1.1	1.3
upper quartile .....	3.7	2.5	2.0	2.4
Women:				
lower quartile .....	1.4	1.0	0.7	0.9
median quartile .....	2.3	2.0	1.4	1.7
upper quartile .....	4.3	3.5	2.6	3.2

and is thus statistically verified. The material is divided into »older» and »younger» pensioners. The border-line was drawn at 45 years. In this distribution of the material also the circumstance just mentioned holds good, i. e. a greater degree of disablement with a shorter period between the last treatment and the investigation date. The same applies to the men also. This is connected with the fact that treatment at the Pensions Board's hospital is as a rule only given to such cases as may be thought to be so amenable to treatment that they might conceivably be capable of work again within a reasonable time. If a case has not improved after one or several periods of treatment to the extent that there is justification for a real hope of a recovery of the capacity for work, no further treatment is allowed, which then usually results in the invalid applying for a pension within a short time. This appears from table 6, which shows that the severer the degree of disablement, the sooner the patients are pensioned. The average period for men of degree 1 was a full two years, on the other hand for degree 3 only about half as long. For women the figures are about the same.

Thus, since, in the great majority of cases, pensions will probably be obtained fairly soon after the last period of treatment, it may be expected *a priori* that an investigation of the connection between the degree of disablement and the period between the date of the pensioning and the date of the investigation will show the same

Table 7.

The distribution of the material over the degrees of disablement in combination with the interval between the date of pensioning and the investigation.

Interval between the date of pensioning and the investigation	Total number = N	of which in degree of disablement					
		1		2		3	
		number	% of N	number	% of N	number	% of N
Men:							
under 5 years	238	41	17.2±2.4	106	44.5±3.2	91	38.2±3.2
5 years and over . . . . .	146	18	12.3±2.7	76	52.1±4.1	52	35.6±4.0
Women:							
under 5 years	406	73	18.0±1.9	136	33.5±2.3	197	48.5±2.5
5 years and over . . . . .	218	18	8.3±1.9	91	41.7±3.3	109	50.0±3.4

result, and this is actually the case (tables 7 and 8). Both tables show that in general the pension was granted earlier for persons coming under degree 3. A slight levelling out between the figures can be discerned, however, which is naturally explained by the fact that a certain time always elapses between the last treatment and the granting of the pension.

Table 8.

The interval in years between the date of pensioning and the investigation

	degree of disablement			
	1	2	3	1—3
Men:				
lower quartile .....	1.8	2.3	2.6	2.3
median quartile .....	3.3	4.0	3.9	3.8
upper quartile .....	5.5	6.5	5.7	6.0
Women:				
lower quartile .....	2.0	2.0	2.5	2.2
median quartile .....	3.5	3.8	3.8	3.7
upper quartile .....	4.4	6.4	5.5	5.4



*Condition.*

It is naturally of great interest, from both the medical and the social points of view, to try to arrive at a conception of the general condition of the rheumatic invalids. The question of the care and treatment of the pensioners is intimately connected with this question.

In the investigation the condition of the pensioners were grouped in 4 degrees, as is seen clearly from table 9. If the group of invalids who can manage for themselves entirely is examined first, it is found, on making a comparison between all the men and all the women, that the men are able to manage for themselves to a considerably greater extent than are the women. The percentage figure for men is  $58.8 \pm 2.5\%$ , and for women only  $39.8 \pm 2.0\%$ . As is seen, the difference is statistically verified.

Table 9.

The condition in different degrees of disablement.

Degree of disablement		Manages entirely alone	Manages partly alone	Cannot manage at all	Manages alone at times	Total
Men:						
1.	{ number.....	43	5	3	7	58
	{ % .....	74.1	8.6	5.2	12.1	100.0
2.	{ number.....	117	39	16	9	181
	{ % .....	64.6	21.5	8.8	5.0	100.0
3.	{ number.....	63	31	23	23	140
	{ % .....	45.0	22.1	16.4	16.4	100.0
1.—3.	{ number.....	223	75	42	39	379 <sup>1</sup>
	{ % .....	58.8	19.8	11.1	10.3	100.0
Women:						
1.	{ number.....	55	20	3	13	91
	{ % .....	60.4	22.0	3.3	14.3	100.0
2.	{ number.....	111	57	29	30	227
	{ % .....	48.9	25.1	12.8	13.2	100.0
3.	{ number.....	81	101	75	46	303
	{ % .....	26.7	33.3	24.8	15.2	100.0
1.—3.	{ number.....	247	178	107	89	621 <sup>1</sup>
	{ % .....	39.8	28.7	17.2	14.3	100.0

<sup>1</sup> For 5 men and 3 women no information as to condition.

If the percentage figures for those who cannot manage for themselves at all are then examined, the conditions are naturally found to be the reverse. Thus, in this case the women are preponderant with  $17.2 \pm 1.5$  %, as against  $11.1 \pm 1.6$  % for the men.

The chief reason why the men were able to manage for themselves after being pensioned to a greater extent than the women is naturally that, even with fairly moderate disablement, men are compelled to give up their work, usually heavy, after which they apply for pensions. The women, who are less frequently breadwinners, evidently try as long as possible to perform their lighter housework to the best of their ability, in spite of increasing disablement. Not until they are no longer capable of doing any useful work worth mentioning in the home do they apply for pensions. When these are obtained, the women are therefore probably in a considerably worse condition than are the men. Another important reason why the pensioned women are more disabled than the men is the circumstance pointed out above, that chronic polyarthritis in women often runs a more rapid and a severer course than in men.

Table 10.

The proportion of rheumatic invalids who require daily help.

Degree of disablement	Total number = N	Number who are helped			
		abs. no. = n	% of N	of which helped by a relative	
				abs. ant.	% of n
Men:					
1	59	15	25.4	12	80.0
2	182	55	30.2	45	81.8
3	143	64	44.8	61	95.3
1—3	384	134	34.9	118	88.1
Women:					
1	91	32	35.2	29	90.6
2	227	98	43.2	85	86.7
3	306	167	54.6	151	90.4
1—3	624	297	47.6	265	89.2

In the matter of the condition of the pensioners, too, the investigation material has been divided into older and younger persons. If the analysis of the material is also extended to cover these groups, it is found that age does not play any considerable rôle. On the whole the percentile distribution over the different condition groups is the same whether the material comprises older or younger persons. It is natural that the capacity to manage entirely without help decreases with an increasing degree of disablement. This circumstance appears clearly from table 9.

Further light is thrown upon the condition of the pensioners, if an investigation is made of the extent to which they require daily help. It appears from table 10 that fully one-third of the men (35 %) and nearly half of the women (48 %) require constant personal assistance. The difference ( $13 \pm 3.1$  %) is statistically verified. As might be expected, the percentage increases with the degree of disablement. For degree 1 the figures 25 % for men and 35 % for women are obtained, for degree 3 45 % for men and 55 % for women.

In the great majority of cases (about 90 %) it is a relative of the invalid who has to give assistance. The figure is the same for men and women.

Nor in this respect are any essential differences shown between the younger and older groups of the material.

### *Capacity for work.*

With the condition of the pensioners is naturally connected their greater or lesser capability of work. With the object of gaining an idea of this, the investigation material was worked up in such a manner that the pensioners who could perform real work were assembled in one group, those who could only take part in the housework, and who thus needed other help for the management of the home in another group; and those who could not do any work at all in a third. From this last group was divided off, further, the small number of pensioners who were in a hospital or institution.

The percentile distribution over the different kinds of work capacity is shown in table 11. If, with the help of this table, a comparative examination is made of the capacity for work as between the sexes, great care must be taken for the work performed by men

Table 11.

The distribution of the material according to the capability for work.

Age group and degree of disablement		Work <sup>1</sup>	Light work in the home	No work	In hospital or a home for invalids	Total
Younger men 1—3	{ number	90	14	65	15	184
	{ %	48.9	7.6	35.3	8.2	100.0
Older men 1—3	{ number	95	7	88	9	199
	{ %	47.8	3.5	44.2	4.5	100.0
Total of men 1	{ number	39	3	13	4	59
	{ %	66.1	5.1	22.0	6.8	100.0
" " " 2	{ number	98	11	61	11	181
	{ %	54.1	6.1	33.7	6.1	100.0
" " " 3	{ number	48	7	79	9	143
	{ %	33.6	4.9	55.2	6.3	100.0
" " " 1—3	{ number	185	21	153	24	383
	{ %	48.3	5.5	39.9	6.3	100.0
Younger women 1—3	{ number	110	65	99	22	296
	{ %	37.2	22.0	33.4	7.4	100.0
Older women 1—3	{ number	95	123	82	25	325
	{ %	29.2	37.9	25.2	7.7	100.0
Total of women 1	{ number	39	37	12	3	91
	{ %	42.8	40.7	13.2	3.3	100.0
" " " 2	{ number	87	67	56	17	227
	{ %	38.2	29.5	24.7	7.5	100.0
" " " 3	{ number	79	84	113	27	303
	{ %	26.0	27.7	37.3	8.9	100.0
" " " 1—3	{ number	205	188	181	47	621
	{ %	33.0	30.3	29.1	7.6	100.0

and women usually differs in nature. If among working women are included also women who manage a home without help, as they indisputably must be, it is found that one-third of the women can be placed in this category. As regards the men, it proves that nearly half of them perform some kind of work. Light work in the

<sup>1</sup> In the case of women, those who manage the home without help have also been placed in this group.

home is performed to a considerably greater extent by the women (30 %) than by the men (5 %), as might have been anticipated. If the two categories are combined, the result is obtained that a somewhat larger proportion of the women do more or less work (c. 63 %) in comparison with the men (c. 54 %).

In the case of the men, it can be established that there is no considerable difference between younger and older men. It appears clearly from the table, however, that the capacity for work decreases with an increasing degree of disablement. In degree 1 twice the number of men work, as compared with degree 3 (66 and 34 % respectively).

Among the women, work or light household work appears to be performed to a somewhat greater extent among the older ones than among the younger. It was stated that 83 % of the women had work or performed light housework in degree 1, and 54 % in degree 3.

Of the men, 24 (6.3 %) and of the women, 47 (7.6 %) were receiving permanent care in homes for invalids or institutions (table 11). The men were distributed fairly evenly over homes for chronic

Table 12.

Percentile proportion of rheumatic pensioners with incomes from their own work only, apart from the pension.

Degree of disablement	Total number <sup>1</sup> = N	of which with incomes from their own work	
		number	% of N
Men:			
1	50	24	48.0±7.1
2	144	56	38.9±4.1
3	109	31	28.4±4.3
1—3	303	111	36.6±2.8
Women:			
1	39	2	5.1±3.5
2	101	8	7.9±2.7
3	123	7	5.7±2.1
1—3	263	17	6.5±1.5

<sup>1</sup> No particulars given for men in 81 cases and for women in 361 cases.

Table 13.

The distribution of the material according to housing conditions.

Age group and degree of disablement		Live with family or parents	Live with brother or sister or near relation	Live with some other person	Live alone	Unknown	Total
Younger men 1—3	{ number	116	18	7	24	20	185
	{ %	62.7	9.7	3.8	13.0	10.8	100.0
Older men 1—3	{ number	137	13	5	25	19	199
	{ %	68.8	6.5	2.5	12.6	9.5	100.0
Total of men 1	{ number	40	4	2	8	5	59
	{ %	67.8	6.8	3.4	13.6	8.5	100.0
» » » 2	{ number	115	18	6	23	20	182
	{ %	63.2	9.9	3.3	12.6	11.0	100.0
» » » 3	{ number	98	9	4	18	14	143
	{ %	68.5	6.3	2.8	12.6	9.8	100.0
» » » 1—3	{ number	253	31	12	49	39	384
	{ %	65.9	8.1	3.1	12.8	10.2	100.0
Younger women 1—3	{ number	202	35	8	32	21	298
	{ %	67.8	11.7	2.7	10.7	7.0	100.0
Older women 1—3	{ number	157	69	10	61	29	326
	{ %	48.2	21.2	3.1	18.7	8.9	100.0
Total of women 1	{ number	52	13	2	19	4	90
	{ %	57.8	14.4	2.2	21.1	4.4	100.0
» » » 2	{ number	132	38	8	34	15	227
	{ %	58.2	16.7	3.5	15.0	6.6	100.0
» » » 3	{ number	175	53	8	40	31	307
	{ %	57.0	17.3	2.6	13.0	10.1	100.0
» » » 1—3	{ number	359	104	18	93	50	624
	{ %	57.5	16.7	2.9	14.9	8.0	100.0

live alone. Table 14 was compiled to elucidate this point. It proved, however, that on the whole those living alone were distributed over the different degrees of disablement similarly to those not living alone. This is true of both men and women. The majority of the pensioners naturally do not live alone, only about one-sixth of both women and men doing so. But, remarkably enough, among

Table 14.

The degree of disablement in pensioners living alone and not living alone.

	Total number = N	of which in degree of disablement					
		1		2		3	
		number	% of N	number	% of N	number	% of N
Men:							
Living alone	49	8	16.3±5.3	23	46.9±7.1	18	36.7±6.9
Not living alone ....	296	46	15.5±2.1	139	47.0±2.9	111	37.5±2.8
Women:							
Living alone	93	19	20.4±4.2	34	36.6±5.0	40	43.0±5.1
Not living alone ....	481	67	13.9±1.6	178	37.0±2.2	236	49.1±2.3

those living alone the severest degree of disablement is met with to approximately the same extent as among those not living alone. Among the men, the proportion with degree 3 is fully one-third, and

Table 15.

The quality of the accommodation.<sup>1</sup>

G r o u p	Own home	Shared home or lodger	Total	of which with poor accom- modation	
Younger men . . . . . {	number	113	52	165	19
	%	68.5	31.5±3.6	100.0	11.5±2.5
Older men . . . . . {	number	165	24	189	22
	%	87.3	12.7±2.4	100.0	11.6±2.3
Total of men . . . . . {	number	278	76	354	41
	%	78.5	21.5±2.2	100.0	11.6±1.7
Younger women . . . . {	number	128	143	271	27
	%	47.2	52.8±3.0	100.0	10.0±1.8
Older women . . . . . {	number	215	77	292	47
	%	73.6	26.4±2.6	100.0	16.1±2.2
Total of women . . . . {	number	343	220	563	74
	%	60.9	39.1±2.1	100.0	13.1±1.4

<sup>1</sup> 24 men and 47 women who are cared for in institutions are not included in the table. Further, no particulars as to the quality of the accommodation were returned in the cases of 6 men and 14 women.

among the women nearly one-half. However, the material is too limited to permit of a more detailed statistical analysis in this respect.

About 21 % of the men and 39 % of the women have not homes of their own. If the older and younger are compared, it is found that the figure is twice as high among the younger in the case of both men and women (table 15).

The quality of the accommodation has been classified as »poor» for 11 % of the men's and 13 % of the women's dwellings (table 15). There is reason to assume that the appraisalment of the quality of the home was tolerant throughout, and therefore the figures given must be considered minimum figures. There is no tangible difference in the matter of the quality of the homes as between those of the older and younger men. On the other hand it appears from the table that among the older women there was a tendency to live in poorer homes than among the younger. No difference as regards the quality of the homes can be established within the different degrees of disablement.

Table 16.

Percentile number of rheumatic pensioners who were stated to be badly looked after.<sup>1</sup>

Degree of disablement	Total number = N	of whom badly looked after	
		number	% of N
Men:			
1	54	2	$3.7 \pm 2.6$
2	171	9	$5.3 \pm 1.7$
3	139	9	$6.5 \pm 2.1$
1—3	364 <sup>1</sup>	20	$5.5 \pm 1.2$
Women:			
1	89	3	$3.4 \pm 1.9$
2	223	6	$2.7 \pm 1.1$
3	300	11	$3.7 \pm 1.1$
1—3	612 <sup>1</sup>	20	$3.3 \pm 0.7$

<sup>1</sup> No particulars on this point in the cases of 20 men and 12 women.



*Care.*

To the question whether the pensioners can be considered well cared for, answers have been given in 976 cases, referring to 364 men and 612 women. The information has been worked up and collocated in table 12. 5.5 % of the men and 3.3 % of the women were stated to be badly looked after (the difference is not statistically verified). No material difference is met with as regards the frequency for older and younger; or as regards the various degrees of disablement.

*Care before pensioning.*

As has been pointed out above, the investigation material comprises only such rheumatic invalids as had received treatment through the instrumentality of K. P. before being granted pen-

Table 17.

The distribution of the material according to the number of periods of treatment in combination with the degrees of disablement.<sup>1</sup>

Treatment, number of periods	Degree of disablement			
	1	2	3	1—3
Men:				
1 .....	26	65	47	138
2 .....	15	56	50	121
3 .....	14	39	32	85
4 .....	4	19	11	34
5 .....	—	2	2	4
6 .....	—	—	1	1
Total .....	59	181	143	383
Average number .....	1.9	2.1	2.1	2.1
Women:				
1 .....	41	71	96	208
2 .....	19	72	94	185
3 .....	23	53	83	159
4 .....	7	26	29	62
5 .....	—	3	3	6
6 .....	—	1	1	2
Total .....	90	226	306	622
Average number .....	2.0	2.2	2.2	2.2

<sup>1</sup> No particulars of the number of periods of treatment given in the case of 1 man and 2 women.

Table 18 a.  
Other illnesses. Men.

	Degree of disablement							
	1		2		3		1—3	
	number	%	number	%	number	%	number	%
Younger men								
No other illness ..	22	75.9	69	75.0	54	84.4	145	78.4
Other illnesses ..	7	24.1	23	25.0	10	15.6	40	21.6
of which heart								
affections ....	0	0	8	8.7	2	3.1	10	5.4
Total .....	29	100.0	92	100.0	64	100.0	185	100.0
Older men:								
No other illness ..	23	76.7	71	78.9	67	84.8	161	80.9
Other illnesses ..	7	23.3	19	21.1	12	15.2	38	19.1
of which heart								
affections ....	2	6.7	5	5.6	3	3.8	10	5.0
Total .....	30	100.0	90	100.0	79	100.0	199	100.0
Total of men.								
No other illness ..	45	76.3	140	76.9	121	84.6	306	79.7
Other illnesses ..	14	23.7	42	23.1	22	15.4	78	20.3
of which heart								
affections ....	2	3.4	13	7.1	5	3.5	20	5.2
Total .....	59	100.0	182	100.0	143	100.0	384	100.0

sions, the average number of treatments appearing from table 17. It is found that every pensioner had received treatment twice on an average. No verified increase in the average number according to the degree of disablement emerges from the material. It is possible, however, that a larger material might show a decided tendency towards a greater number of periods of treatment in the case of severer degrees of disablement. However, if there is such an increase it appears to be inappreciable.

#### *Other illnesses afflicting the pensioners.*

Comparatively often the pensioners were suffering from some other illness as well as the rheumatic affection (tables 18a and b). This is the case in 20 % of the men and 25 % of the women. Heart

Table 18 b.  
Other illnesses. Women.

	Degree of disablement							
	1		2		3		1—3	
	number	%	number	%	number	%	number	%
Younger women:								
No other illness:	23	56.1	93	79.5	122	87.1	238	79.9
Other illnesses ..	18	43.9	24	20.5	18	12.9	60	20.1
of which heart								
affections ....	8	19.5	13	11.1	6	4.3	27	9.1
Total .....	41	100.0	117	100.0	140	100.0	298	100.0
Older women:								
No other illness ..	35	71.4	77	70.0	119	71.3	231	70.9
Other illnesses ..	14	28.6	33	30.0	48	28.7	95	29.1
of which heart								
affections ....	4	8.2	11	10.0	14	8.4	29	8.9
Total .....	49	100.0	110	100.0	167	100.0	326	100.0
Total of women:								
No other illness ..	58	64.4	170	74.9	241	78.5	469	75.2
Other illnesses ..	32	35.6	57	25.1	66	21.5	155	24.8
of which heart								
affections ....	12	13.3	24	10.6	20	6.5	56	9.0
Total .....	90	100.0	227	100.0	307	100.0	624	100.0

disease is the most usual illness met with and is reported in 5.2 ( $\pm 1.1$ ) % of the men and 9.0 ( $\pm 1.1$ ) % of the women. (The difference is probable). There is no difference in the frequency of other illnesses as between the younger and the older persons, either in the case of heart disease or other illnesses. On the other hand, it seems that the frequency is higher for the slighter cases of polyarthritis. The increase is statistically verified only in the group of younger women, but reappears in the majority of the groups, both if we consider the frequency of heart disease taken by itself and of other illnesses. The explanation of this will probably be that just the occurrence of other illnesses contributed towards the person in question being granted a pension, so that the frequency of other illnesses should be greater among the less seriously disabled.

Next to heart disease, tuberculosis is the commonest disease in this material. Further, among women, neuroses and organ and nerve diseases are not very uncommon.

### Conclusions.

It now remains to examine in what respects the investigation can lead to measures for improving the general circumstances of the rheumatic invalids. As was mentioned by way of introduction, the questions formulated before the investigation could certainly not all be answered sufficiently clearly or satisfactorily. For this a considerably more comprehensive and more detailed investigation would have been necessary. This is true especially as regards the question whether the invalids are well cared for or not. It is manifest that, in this respect, the investigation is of very limited value, owing to the all too summary formulation of the questions in the questionnaires sent out, and the usually equally summary answers. To obtain a clearer conception of the nature of the care given, a detailed questionnaire would have been necessary, the filling in of which would probably have involved all too great demands on the good-will and time of the Chairmen of the Pensions Committees. Nevertheless, certain conclusions can be drawn in this respect from the investigation. Only 5.5 % of the men and 3.1 % of the women were stated to be poorly looked after. That these figures do not reflect the actual state of things, but are too low, appears, *inter alia*, from the circumstance that nearly 13 % of both women and men with degree 3 of disablement lived alone and were thus compelled to manage for themselves, in spite of their severe disablement (table 13). Further, if it is borne in mind that the people here in question belong socially to the worst circumstanced in the community, one may probably venture the assumption that a great number of the invalids living with their families, relations or friends, i. e. the great majority (77 % of the men and 70 % of the women) are not well looked after, even though this is not directly stated by the respective Chairmen of the Pensions Committees.

It might have been expected that a considerable number of the rheumatic invalids would have been nursed in homes for chronic invalids or homes for the aged. As has been shown above, however, only c. 7 % of the total number of invalids were in such institutions.

The reasons for this will probably be both a shortage of places in some hospitals for chronic invalids, and also the circumstance that, for psychological reasons, rheumatic invalids prefer to remain in their home milieu, however inconvenient the housing conditions.

The problem of whether all the rheumatic pensioners are to be considered as definitively disabled, or whether, with treatment, some of them might be helped to improved health and increased earning capacity is elucidated to some extent by the investigation. It has proved that 37 % of the men had incomes in the form of wages apart from the pension. The illness of these invalids must thus be considered fairly stationary, and their general condition must be assumed to have been relatively good, since they managed to provide for themselves by their own efforts, even though with the help of the pension. Undoubtedly the condition of a large proportion of these invalids could be improved by means of medical attention and the therapeutic possibilities which are now available, so that they might arrive at full wage-earning capacity. Considering the effect of the modern methods of treatment — I am thinking more particularly of the progress of chemotherapy in the treatment of chronic polyarthritis and of the possibilities of orthopedic treatment in improving the function of the organs of movement — it will probably not be too much to assume that a large proportion of the rheumatic invalids now entirely incapable of work, would be able to contribute more or less towards their own support by means of work, if they could have the benefit of the necessary treatment.

The measures for improving the circumstances of the rheumatic invalids which appear most urgent at the present time, are in my opinion the following:

- 1) An increased number of places in homes for chronic invalids for the incurably disabled.

- 2) Possibilities for the rheumatics who have already been pensioned to receive necessary hospital treatment. Under the present regulations for the medical activities of the Pensions Board, treatment can only be given to such invalids as may be expected to become entirely or partially capable of work after a relatively short period of treatment. After pensions have been granted, treatment cannot in general be given to the sufferer at the Pensions Board's institutions. This circumstance, which is conditioned by insurance-technical factors, is not compatible with medical and social ethics.

So long as other nursing possibilities do not exist, therefore, the Pensions Board's hospital should on the whole be available for all who, according to medical opinion, might conceivably be improved thereby.

3) The establishment of a dispensary organisation for rheumatic invalids, which is probably necessary, both for the proper care of the rheumatic invalids, and for the rational treatment of rheumatic persons in general.

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State University, Leyden, The Netherlands).

## **The part of postmortal autolysis in the necrosis of the liver parenchyma in subacute atrophy.**

By

**CORNELIA van BEEK and A. J. CH. HAEX.**

(Submitted for publication May 11, 1943).

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In 1919 Umber (1) pronounced the opinion that the flaccidity of the liver observed in acute atrophy is due to postmortal digestion. He supposed that the autolysis of the liver parenchyma, which in this disease begins already during life, proceeds after death with unusual speed, so that the organ, which till the moment of death would be firm, is found to be flabby at the autopsy. Umber based this view on an observation made on the liver of a female patient, whose illness was clinically diagnosed as acute yellow atrophy. On the 34th day of her illness she could leave her bed, but seven days afterwards and then again five days later she suffered from severe attacks of pain accompanied by jaundice. As cholelithiasis seemed possible, laparotomy was carried out, but no stones were found. The liver felt firm, and showed atrophic parts of a red colour side by side with purple prominences. For the microscopical examination a small piece was resected. Atrophic parts with proliferating bile-ducts appeared to alternate with regenerating parenchyma. The firmness of the liver led to the conclusion quoted above. Umber overlooked however that the organ at the time of the operation could no longer be regarded as a good example of acute or subacute atrophy of the liver, for between the disease had reached its culminating-

point and the operation more than a month, and since the onset of jaundice even two months had elapsed. Regeneration already had taken place on a large scale. That the liver at the moment of the laparotomy in this case felt firm, allows in our opinion no conclusion with regard to its consistency during life in the acute or subacute stage of the disease. Umber's patient was cured. Although the example on which Umber based his hypothesis, can therefore not be considered appropriate, his view nevertheless was a sound one, and finds support in our own observations.

Umber's conclusion was criticized by Fraenkel (2). The latter rightly remarked that to prove Umber's hypothesis an investigation of the liver both before and after death is required.

Fraenkel himself could test this hypothesis in two cases, but he was unable to find any difference in the microscopical aspect of the liver ante et post mortem: the necrosis had not increased after death. He also pointed out that the consistency of the liver varies according to the stage of the disease between flabby, limp-elastic and more or less tough. According to Versé (3) the consistency moreover depends on the moment at which the autopsy is performed: within two hours after death the ochreous parts in his case still felt firm, but a few hours later, owing to the postmortally increased autolysis, they became flabby.

Hanser (4) too could compare the condition of the liver ante et post mortem in two patients who died of subacute atrophy of the liver. This investigator performed biopsy at laparotomy and found intact liver parenchyma with normally staining nuclei. At the autopsy, however, the structure of the liver was no longer recognizable, and the nuclei stained but poorly or not at all. Hanser concluded that the liver, which intravitaly was already injured, postmortally was subject to a vigorous autolysis, and that the necrosis which had taken place before death, was therefore less pronounced than the autopsy suggested.

Olivet (5) performed aspiration biopsy of the liver 14 hours before death on a patient suffering from acute atrophy of the liver and states that at the autopsy the deviations had greatly increased.

Roholm and Iversen (6), to whom we owe the revival of the practice of aspiration biopsy of the liver, also compared the liver parenchyma obtained by aspiration from a patient suffering from subacute atrophy 16 hours before and 10 hours after death. The first



specimen showed degeneration of the parenchyma whose nuclei however stained normally, the second one necrosis of the parenchyma and Roholm and Iversen therefore concluded that in subacute atrophy the complete necrosis of the liver parenchyma observed at the autopsy, is mainly due to postmortal autolysis.

From the reports published by Fraenkel, Hanser, Olivet and Roholm and Iversen it is clear that in each case a comparison was made between the histopathology of the liver as it was found at least 10 hours before death with that at least 10 hours after death, but that nowhere the condition just after death was examined. This seems to us a matter of fundamental importance.

Authors	Examination of the liver in cases of subacute atrophy	
	Number of hours ante mortem	Number of hours post mortem
Fraenkel (1920) ..	a. 10 (laparotomy)	a. 12 (autopsy)
	b. < 24 »	b. 20 »
Hanser (1921) ....	a. 6 »	a. 30 »
	b. 20 »	b. 24 »
Olivet (1926) ....	14 (aspiration biopsy)	13 »
Roholm and Iversen (1939) ....	16 (aspiration biopsy)	10 (aspiration biopsy)
Van Beek and Haex (1943) .....	—	$\frac{1}{2}$ and $6\frac{3}{4}$ » » and $18\frac{3}{4}$ (autopsy)

Our own observations are the following.

A man, 68 years of age, fell ill with jaundice; he felt dull, somnolent and mentally confused. Five days after the onset of his illness the patient was admitted to the Academical Hospital, Leyden. As the result of a comprehensive examination the illness was diagnosed as (sub)acute atrophy of the liver. The sopor continually increased, and the man died 12 days after the onset of his illness. Various reasons prohibited an ante mortem examination of the liver.

Half an hour after his death an aspiration biopsy was performed on the right lobe of the liver according to the technique described by Iversen and Roholm (7). The remnants of the liver parenchyma showed sharply defined cells with normally staining nuclei and a



Fig. 1.  $\frac{1}{2}$  hour after death;  $\times 100$ .

The liver parenchyma shows sharply defined cells with clearly stained nuclei

minutely granulated protoplasm without vacuoles (fig. 1). Between these patches of parenchyma which were still in good condition, there were areas where not a single liver cell was left, but where the connective tissue and, to an even greater extent, the bile-ducts were seen to proliferate, and where at the same time an infiltration with polymorphonuclear leucocytes and lymphocytes was noticed. In these parts signs of hyperemia and hemorrhagia moreover were present.  $6\frac{3}{4}$  hours after death another biopsy was performed. Now the remnants of the parenchyma had partially lost their cohesion, and compared with the tissue obtained  $\frac{1}{2}$  hour after death, the nuclei did not stain so well, and the protoplasm was more cloudy (fig. 2). The next morning we tried once more to perform an aspiration biopsy, but owing to the extensive postmortal digestion, which in the meantime had made unusual progress, we did not succeed. For this reason at the autopsy, which took place  $18\frac{3}{4}$  hours after death, next to the part where the biopsies had been performed, a small piece of the liver was resected.

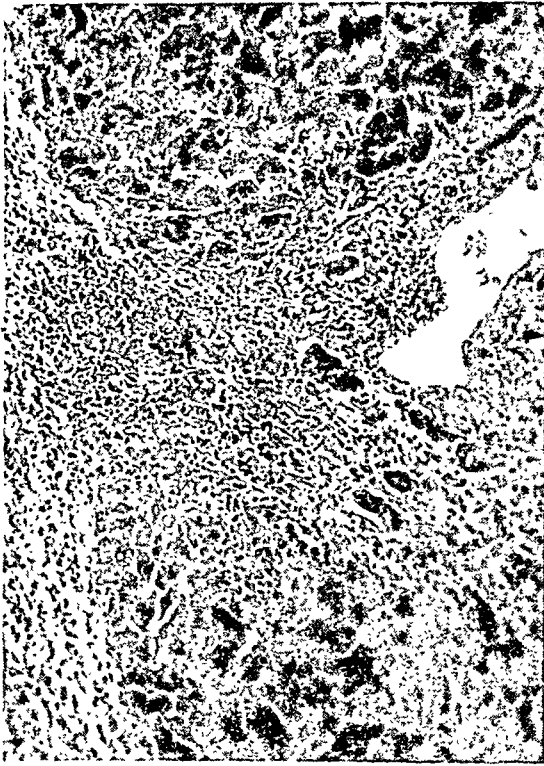


Fig. 2.  $6\frac{3}{4}$  hours after death;  $\times 100$ .

The liver parenchyma is partly disintegrated; the nuclei stain less clearly and the protoplasm has become more cloudy.

The liver itself was greatly reduced in size (weight: 575 g), and appeared very flabby; the left lobe especially was considerably diminished in size, and showed a green discoloration, whereas the liver structure was no longer recognizable. This lobe was rather tough than limp. The right lobe on the other hand was flabby, and showed a somewhat uneven surface with ochreous prominences in which the liver structure was still preserved alternating with depressed grey-blue parts without structure. The cut surface showed in the right lobe several orange-brown foci in which the liver structure was preserved alternating with shrunken structureless red-brown parts; in the left lobe there was on section no indication of a lobular pattern. The edge of the liver was clearly defined, and in the shrunken, structureless parts the wrinkled capsule curved inwards.

The microscopical examination revealed that the areas which macroscopically appeared ochreous, consisted of almost completely

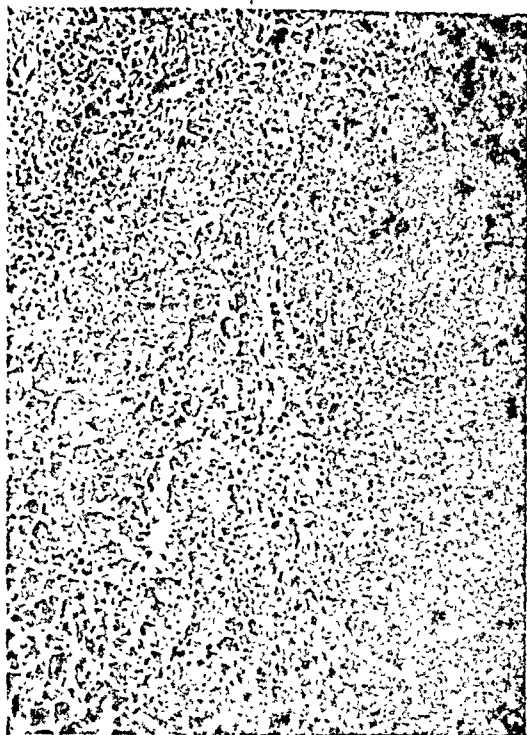


Fig. 3. 18  $\frac{3}{4}$  hours after death;  $\times 100$ .

The liver parenchyma is entirely disintegrated, and has become necrotic.

necrotic and disintegrated liver parenchyma (fig. 3). The nuclei of the leucocytes and of the cells of the bile-ducts were the only ones that still could be stained. The ochreous colour was not due to the presence of fat (reaction with Sudan III negative) but to that of bile pigment in the liver cells themselves, the bile-capillaries and the Kupffer cells. In the left lobe and in those parts of the right one which macroscopically appeared shrunken and red-brown, no parenchyma could be detected, but the tissue appeared to consist of densely crowded triangles of Kiernan, detritus, Kupffer cells filled with fat (reaction with Sudan III positive), young connective tissue, proliferating bile-ducts and extensive hemorrhages. As the parenchyma in these parts had disappeared completely during life, the portal spaces of Kiernan came nearer to each other. This should be kept in mind when considering the proliferation of the connective tissue. The diagnosis based on the results of the gross and microscopic examination at the autopsy would have been:

subacute atrophy of the liver with complete necrosis of the parenchyma; study of the liver tissue taken respectively  $\frac{1}{2}$  and  $6\frac{3}{4}$  hours post mortem, however led to the following conclusion:

The liver parenchyma that in our case of subacute atrophy at the moment of death still remained (macroscopically visible as ochreous prominences) was subject to an unusually vigorous postmortal digestion, and for this reason the necrosis appeared at autopsy more extensive than it was at the moment of death. That the necrosis observed at necropsy is due for a great part to postmortal autolysis, — a thesis brought forward by Umber, Hanser, and Roholm and Iversen, but not fully demonstrated by these authors, because they failed to examine the liver at the moment of death — finds therefore support in the results of the investigation detailed above.

By the aid of the staining method of Best, the specimen being fixed in 96 per cent alcohol, the presence of glycogen could not be detected in any of our slides. The results of the micro-glycogen-determination were:  $\frac{1}{2}$  hour post mortem 0.44 g per cent;  $6\frac{3}{4}$  hours post mortem 0.42 g per cent;  $18\frac{3}{4}$  hours post mortem 0.22 g per cent. These figures may be taken as a quantitative expression of the glycogen deficiency of the liver in a case of subacute atrophy.

### Summary.

By comparing the tissue obtained by aspiration biopsy respectively  $\frac{1}{2}$  and  $6\frac{3}{4}$  hours after death from the liver of a man who had died of subacute atrophy, with liver tissue resected at the autopsy  $18\frac{3}{4}$  hours post mortem, it was found that the diffuse necrosis which was observed at necropsy was mainly due to postmortal autolysis. The liver parenchyma that was not destructed by the intravital autolysis (macroscopically visible as ochreous prominences) showed a well-defined structure and normally staining nuclei immediately after death, but it disintegrated very rapidly as a result of postmortal digestion.

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## Experimental Investigations on the Function of the Autonomic Nervous System During the Acute Phase of Poliomyelitis.

By

KNUD LUNDBÆK.

(Submitted for publication March 24, 1943).

Since the establishment of the pathological process in the spinal cord in cases of poliomyelitis, this disease was generally taken to be an entirely motor affection (Charcot, 1880).

Long before that time, however, it was fully realized that autonomic disturbances in the paralyzed extremities were common phenomena in the late stages of the disease (HEINE, 1860; Laborde, 1864). But the autonomic phenomena in the beginning of the disease had received only slight attention — as is evident, for instance, from the fact that even as late as in Wickman's monograph (1907) paralysis of the gastro-intestinal tract and the urinary bladder are stated to be rare.

Only in recent years has it been appreciated that transitory autonomic symptoms are common in the first phase of poliomyelitis. These phenomena, as is well known, include the always transitory paralysis of the bladder and intestine (present in 30—40 % of the 386 cases studied by Toomey, 1933), tachycardia, the infrequent abnormalities of the pupil (Ehlers, 1936), and the sudden deaths from bulbar vasomotor collapse or respiratory paralysis.

Of experimental studies on the function of the autonomic nervous system in the acute stage of poliomyelitis only very few have been published. In some cases Kuhlmann & Otto (1939) found an

abnormal dermatographism of the skin regions corresponding to the paralyzed segments. Jungeblut & Resnick (1936) performed glucose tolerance tests on poliomyelitic monkeys and found the blood sugar curves abnormally high and prolonged, which might perhaps be attributable to some autonomic disturbance. As these authors have not taken the diet of the monkeys into account, however, it seems more likely that their findings are attributable to a reduction in the carbohydrate intake owing to anorexia in the sick monkeys.

The present studies are aimed to demonstrate the autonomic abnormalities by means of two methods of examination: Tests with indirect heating and examination of postural reflexes.

### *Pathological Anatomy.*

The pathologic-anatomical process in the acute phase of poliomyelitis consists chiefly in a transitory infiltration with lymphocytes and the irreparable neuronophagia. The lymphocytic infiltrations can be seen everywhere in cross-sections of the cord, up to the diencephalon, in spinal ganglia and in peripheral autonomic ganglia. In the spinal cord, neuronophagia takes place chiefly in the anterior horns, less frequently and less extensively in the lateral horns. In the superior parts of the central nervous system neuronophagia is seen just as often in as outside the nuclei of the motor cranial nerves [Hechst (1925), Covell (1932), Pette, Demme & Környey (1932), Pette (1942)]. A few authors think they have been able to demonstrate slight damage to the nerve-cells in peripheral autonomic ganglia too [Marinesco, Manicatic & State-Draganesco (1929), Mouriquand, Dechaume, Sedallian & Morin (1930)].

### *Skin Temperature Curves on Indirect Heating.*

Changes in the skin temperature of a hand or foot on heating of another extremity have been described by several authors — *e. g.*, Lewis & Pickering (1932), Uprus, Gaylor & Carmichael (1936) — and investigated in particular by Vanggaard (1941). Vanggaard found, under standardized experimental conditions, that immersion of both lower extremities in water with a temperature of 42–44° produced an increase in the temperature of the fingers of about ten degrees, when the fingers had been chilled beforehand. This rise in the skin temperature appeared after a latent period of 1.5–21.5



Asmussen, Hohwü Christensen & Marius Nielsen (1939) have made a thorough investigation of the mechanism in the hemodynamic variations due to changes in posture. They arrived at the result that the changes in pulse rate are brought about by changes in the arterial pressure that arise on shifting of the blood to or from the lower extremities. In addition, these authors have demonstrated that in the passively erect posture, even with a rise in pulse rate the blood pressure can be maintained only through vasoconstriction in the splanchnic field.

Whether the converse holds true, *i. e.*, whether the change to a posture with the head down is also associated with »another link» in the compensatory mechanism — that is, a vasodilatation — is still unsettled but it seems not improbable.

As is well known, poliomyelitis is often associated with symptoms of a bulbar lesion, the histological substrate of which has been mentioned already. But also in cases which present no noticeable symptoms of bulbar origin, it seems reasonable to imagine that there may be a more or less pronounced, possibly transitory, involvement of bulbar centers. It is possible, therefore, that examination of the reaction to postural changes in patients with acute poliomyelitis might reveal some signs of damage to the reflex center in the medulla oblongata or to lower autonomic centers.

Here an account will be given of a number of tests of this kind carried out on patients with severe poliomyelitis, in part with bulbar symptoms. As it was to be expected, that the tipping of the patient, with his legs hanging down, in the presence of impaired reflexes might lead to a fall in blood pressure that perhaps would be difficult to control, it was decided — except in one case — merely to tip the head downwards (45—60°). From the following it will be evident that this procedure possibly implies also some theoretical advantages.

### *Results.*

In the following a review will be given of the results of the indirect heating tests and examinations of postural reflexes in the individual patients. The outcome of the examinations of postural reflexes is recorded schematically in Table 1.

Table 1.  
*Postural Reflex Examinations.*

Case No.	Initials of the patient	Tipping with head up or down	Blood pressure			Pulse rate		
			Before exam.	During exam.	Difference	Before exam.	During exam.	Difference
Survivors.								
1	L. B.	Down	100	105	+5	83	84	+1
2	G. P.	Down	110	110	0	110	103	—7
3	G. N—J.	Down	130	130	0	120	116	—4
4	H. O.	Down	120	120	0	99	100	+1
Dead.								
10	T. J.	Down	110	135	+25	86	64	—22
11	M. S.	Down	145	165	+20	95	72	—23
		Up	165	130	—35	92	104	+12
12	A. D.	Down	165	165	0	88	104	+16
13	B. J.	Down	120	120	0	120	126	+6
14	B. A.	Down	90	100	+10	122	120	—2

In each case a brief account will be given of the state of the patient at the point of time when these examinations were carried out, giving merely the positive data. In the cases that terminated fatally an abstract will be given of the relevant parts of the autopsy records<sup>1</sup>.

The »days of illness» are reckoned from the first day with meningeal symptoms, without regard to the possible »preliminary illness» (Pette, 1942).

*Case 1 (L. B.).*

The first indirect heating test was performed on the 8' day of illness. Temperature 37.4°. Pulse 80. At that time, severe paralyzes had appeared: total paralysis of the lower extremities and the musculature of the abdomen and chest, subtotal paralysis of the upper extremities. The patient was lying in respirator. The bladder and intestine were paralyzed.

The skin temperature curve obtained for the extremity examined in this experiment is shown in Fig. 1. Indirect heating for 30 min. gave no rise in temperature. The heating was then supplemented with an electric heat-pad applied to the chest and two hot water bottles. In the following 75 min. there was only a transitory slow rise of about 1 degree, and this was accom-

<sup>1</sup> I am obligated to Dr. Erna Christensen for the histological examination and description of the specimens.

panied by a transitory sweating of the face, and the patient complained of nausea. The experiment was repeated on the following day when the condition of the patient was unchanged, except that there now had been spontaneous urination for the first time. The intestinal paralysis persisted unchanged. This time, besides immersion of one arm in the water-bath two electric heat-pads and 3 hot water bottles were applied at once. No rise of the skin temperature of the hand examined appeared in 50 min.

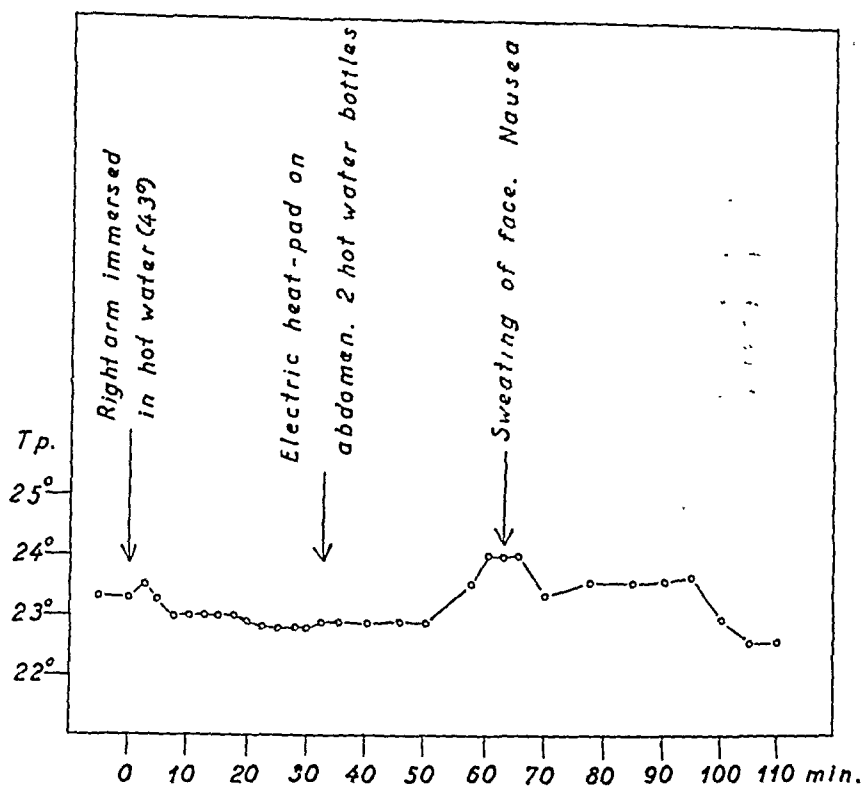


Fig. 1. Case 1. Indirect heating on 8' day of illness.

On the 29' day of illness, after the paralysis of the bladder and intestine had disappeared some time before, a new test was made with indirect heating. At this time the temperature and pulse were normal and the patient was now lying in a bed. The respiration was chiefly auxiliary and diaphragmatic but there was perhaps also faint thoracic respiration. The other pareses were unchanged. — Now a normal vascular reflex was recorded, After 7.5 min. there appeared an abrupt rise in the skin temperature of the hand examined from 25° to about 32°. Then the heated hand was immersed in a water-bath with a temperature of 11°, and in response hereto the other hand showed a more gradual fall in temperature, but on additional chilling of the body the skin temperature fell below the initial level (Fig. 2).

In order to ascertain whether differences in the covering of the patient in the respirator and in the bed played any role in the outcome of the test, the experiment was repeated on the 33' day of illness, with the patient being placed in the respirator again for a few hours before the test. Under these conditions, too, a normal vascular reaction was observed. The latent period was a little longer, but the rise in temperature was rather more abrupt than in the preceding experiments.

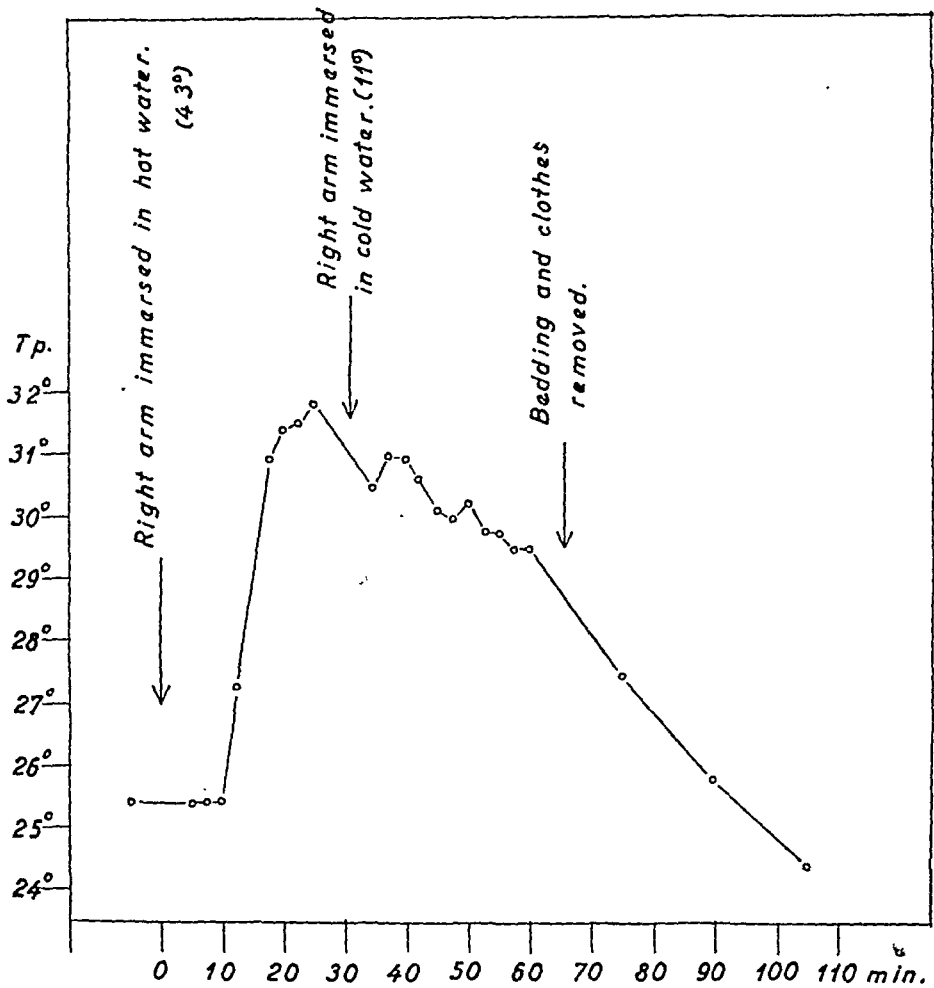


Fig. 2. Case 1. Indirect heating on 29' day of illness.

The postural reflex examination was carried out on the 8' day of illness. It showed no definite abnormality.

#### Case 2 (G. P.).

The first indirect heating test was performed on the 5' day of illness. Temperature 37.9°. Pulse 100. — There was total paralysis of both lower extremities, and subtotal paralysis of both upper extremities, as only the

hands and fingers were able to move a little. In addition, there were paralysis of the abdominal and thoracic muscles, and paralysis of the intestinal bladder. The patient was lying in respirator.

Indirect heating gave no rise in the skin temperature in 40 min.

The experiment was repeated on the 47' day of illness. Now the paralysis of both lower extremities was only subtotal, and there was some function of the abdominal musculature, besides a fairly good function of the intercostal and cervical muscles. The respiration was sufficient. The bladder and bowels were functioning normally.

This time the test gave an abrupt normal rise in the skin temperature of the examined hand, after a latent period of only 2.5 min.

The postural reflex examination was performed on the 6' day of illness. It showed normal conditions.

### *Case 3 (G. N-J.).*

The first indirect heating test was performed on the 7' day of illness. Temperature 38°. Pulse 120. There was total paralysis of the musculature of the thighs and abdomen, subtotal paralysis of the muscles of the leg, intercostal muscles and musculature of the neck. Further, the muscular power of both upper extremities was greatly reduced throughout. The patient was lying in respirator. There was paralysis of the intestine, together with difficulty in urination, but not total paralysis of the bladder.

The test showed no rise in the skin temperature of the examined hand — on the contrary there was a gradual fall in temperature of about 2 degrees.

The experiment was repeated on the 42' day of illness; now the quadriceps femoris, on both sides, was capable of some, albeit slight, mobility; the function of the crural and abdominal muscles as fairly good; and the muscular power of the neck and upper extremities was reduced but little. The respiration was sufficient. The bladder and bowels were functioning normally. This time, the test showed an extraordinarily abrupt and high rise in the skin temperature. After a latent period of only 2.5 min. the skin temperature of the examined hand rose more than 10 degrees in 15 min.

The postural reflex examination was performed on the 7' day of illness, and showed no abnormality.

### *Case 4 (H. O.).*

An indirect chilling test was performed on the 9' day of illness. Temperature 39.3°. Pulse 100. — There was paralysis of both deltoids and of the right triceps, while the muscular power of the right biceps was lowered. There was also paresis of the cervical musculature, the patient being unable to raise his head from the pillow. In addition, facial paralysis on the left side, paralysis of the right trapezius, and paralysis of the right half of the palate, accompanied by slight difficulty in swallowing. No paralysis of the bowel or intestine.

Indirect chilling (11—13°) was not followed by any fall in the skin temperature of the examined hand in 40 min. — on the contrary, there was a small initial rise of 3 degrees, followed by an undulating plateau.

The postural reflex examination, on the 9' day of illness, showed no definite abnormality.

*Case 5 (J. R.).*

The first indirect heating test was performed on the 9' day of illness.

In this case the development of paralysis proceeded at an uncommonly slow rate, and after the culmination of the pareses, improvement commenced almost at once. On the 7' day of illness there was almost complete paralysis of both lower extremities and of the left upper extremity, while the muscular power of the right upper extremity was impaired. There was paralysis of the bladder but no definite paralysis of the intestine. On the day of the test, the 9' day of illness, the mobility of both arms and feet had already become a little better, and there was a slight function of the quadriceps femoris on both sides, but the paralysis of the bladder persisted unchanged. Temperature 38.0°. Pulse 80.

The indirect heating in the usual water-bath gave no rise in the skin temperature of the examined leg in 42.5 min. Then an electrical heat-pad was applied to the chest, and now the skin temperature showed a rise of normal abruptness.

The experiment was repeated on the 23' day of illness. Now the condition of the patient was considerably improved, as she was capable of flexion, albeit slight, in both knee joints, and the right upper extremity showed only a slight decrease in muscular power. The function of the bladder, the temperature and pulse rate were normal. This test gave a normal rise in the skin temperature of the foot, on heating in the usual manner, after a latent period of 22.5 min.

*Case 6 (E. M.).*

The first indirect heating test was performed on the 13' day of illness. Temperature 36.7°. Pulse 60. — There was total paralysis of the lower extremities and the abdominal musculature. The muscular power of the upper extremities was lowered a little. There was still paralysis of the bladder, which in this case persisted unusually long, as spontaneous urination did not return till the 18' day of illness.

The examination showed a curve for the skin temperature as presented in Fig. 4: a very slow rise, in spite of protracted and, finally, massive heating. This curve can not with certainty be said to be abnormal, but its form deviates markedly from the usual, almost instantaneous, rise in the skin temperature on indirect heating.

The experiment was repeated on the 27' day of illness. Now the paralysis of the bladder had disappeared, but otherwise the condition of the patient was rather unchanged. As shown in Fig. 5, this time the test gave a considerably more abrupt rise in the temperature curve.

*Case 7 (P. H.).*

An indirect heating test was performed on the 5' day of illness. Temperature 37.6°. Pulse 79. — There was subtotal paralysis of the cervical musculature, the right upper extremity and both lower extremities; the muscular power of the left upper extremity was lowered greatly. In addition, there was paralysis of the bladder and intestine.

The test showed a normal abrupt rise in the skin temperature of the examined leg after a latent period of 7.5 min.

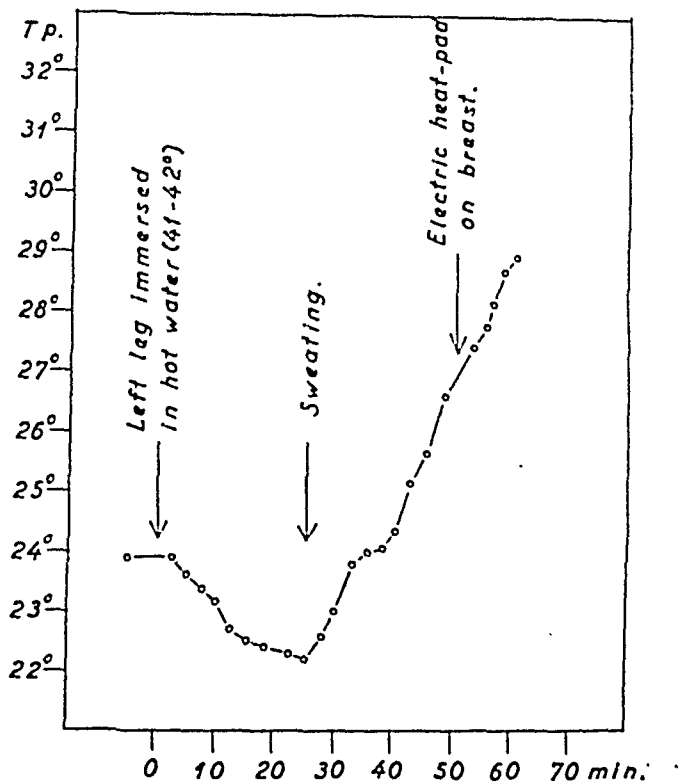


Fig. 3. Case 6. Indirect heating on 13' day of illness.

*Case 8 (O. P.).*

An indirect heating test was performed on the 7' day of illness, when the temperature and pulse were normal. There was subtotal paralysis of both thighs, still, he was able to raise one knee a little from the mattress and contract the muscles of the other thigh but feebly. The muscular power of the legs and left forearm was lowered a little. There was complete paralysis of the bladder, no paralysis of the intestine.

The test showed a normal rise in the skin temperature of the foot examined after a latent period of 17.5 min.

*Case 9 (J. Aa.).*

An indirect heating test was performed on the 13' day of illness, when the temperature and pulse were normal. There was almost total paralysis

of the right upper extremity, slight impairment of the power of the left triceps. No other pareses. The bladder and intestines functioned normally.

Indirect chilling, followed by indirect heating, gave a normal fall in the skin temperature, followed by a normal rise on the extremity examined (the paralyzed right arm).

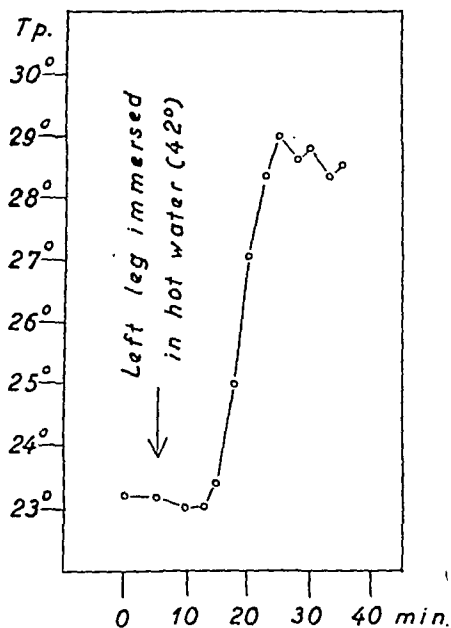


Fig. 4. Case 6. Indirect heating on 27' day of illness.

*Case 10 (T. J.).*

Postural reflex examination on the 3' day of illness. Temperature 39.4°. Pulse 88. — There was paralysis of the cervical musculature. In addition, facial paralysis on the right side and total paralysis of deglutition. No paralysis of the bladder or intestine.

On tipping the head downwards, there appeared a rise in the blood pressure and a fall in the pulse rate.

On the following day the patient suddenly became very ill. The respiration became shallow and gasping, and then it ceased after a few minutes. The pulse was good and strong till shortly after cessation of breathing.

*Abstract from the Autopsy Record (Histol. 21971):*

*Upper part of the medulla oblongata:* Accumulations of lymphocytes are seen beneath the 4' ventricle, localized to clusters of nerve-cells. Several nerve-cells have been destroyed, others show chromatolysis. Oedema and perivascular accumulation of lymphocytes in the olive.

*Medulla oblongata, corresponding to coll. fac.:* Moderate inflammation. Several of the cells in the nucleus of the facialis are unaffected. The changes are most pronounced in the small clusters of nerve-cells lateral hereto. The olive appears normal.



*Medulla oblongata, corresponding to the tip of the 4' ventricle:* Inflammatory phenomena corresponding to a part of the nucleus of the hypoglossal nerve, on one side. But the changes are more pronounced in the areas lateral hereto, corresponding to the n. ambiguus. Perivascular lymphocytic infiltration here and there in the olive.

*Cervical cord:* Moderate perivascular round-cell infiltration and oedema of the white substance. Round-cell infiltration and neuronophagia of the anterior horns.

*Case 11 (M. S.).*

Postural reflex examination on the 6' day of illness. Temperature 38.6°. Pulse 72. At that time there was total paralysis of the upper and lower extremities and of the thoracic musculature; marked impairment of the power of the abdominal musculature. The patient was lying in respirator. He was a little hazy and had difficulty in speaking, but there was no definite paralysis of any cranial nerves. The bladder was completely paralyzed.

On tipping the head downwards, there appeared a considerable rise in the blood pressure and fall in the pulse rate. On tipping the legs downwards — as was done in this case only — there was a fall in the blood pressure and rise in the pulse rate.

The state of the patient was getting worse steadily, and he died on the same day, with signs of vasomotor collapse.

*Abstract from the Autopsy Record (Histol. 21902):*

*Hypothalamus:* Hyperemia, perivascular and diffuse lymphocytic infiltrations; here and there, degenerative changes in the nerve-cells. The changes are most pronounced paraventricularly.

*Medulla oblongata, corresponding to the tip of the 4' ventricle:* Here and there, marked perivascular accumulation of lymphocytes. The nucleus of the hypoglossal nerve is relatively well preserved, but the region lateral hereto shows oedema, perivascular lymphocytic infiltration and degenerative changes in the nerve-cells. In the olive, the nerve-cells are moderately swollen, with eccentric nuclei; but no lymphocytic infiltration is seen here.

*Cervical cord:* Moderate perivascular lymphocyte and plasma-cell infiltration in the white substance. On one side, the anterior and posterior horns show infiltration with lymphocytes and degeneration of the nerve-cells.

*Case 12 (A. D.).*

Indirect chilling test on the 5' day of illness. Temperature 38.1°. Pulse 64. — There were extensive paralyses, the lower extremities being almost completely paralyzed, the abdominal musculature and the lower intercostal muscles totally paralyzed. In addition, the muscular power of the upper extremities and the neck was lowered; and there was diplopia. Total paralysis of the bladder and intestine. There was a slight difficulty in breathing, but the respirator was not yet required.

Indirect chilling (13°) gave an initial fall in the skin temperature of the examined hand, amounting to 2 degrees, which was followed by an undulating plateau round the level of the initial value for 30 min.

Postural reflex examination was performed on the 5<sup>th</sup> day of illness. No change in the blood pressure was observed, but a considerable rise in the pulse rate. The significance of this result will be mentioned later.

On the day after the examination, the state of the patient was aggravated, and the breathing became shallow. The patient was now placed in respirator. Two days later, his condition was worse, with increasing cyanosis, and he died suddenly, with signs of vasomotor collapse.

*Abstract from the Autopsy Record (Histol. 21914):*

*Hypothalamus, just anteriorly to the mammillary body:* Degenerative changes in the nerve-cells, oedema, here and there perivascular infiltration with lymphocytes.

*Hypothalamus, middle part of the mammillary body:* As the preceding section; in addition, a few entirely normal cells, and a few that have undergone complete neuronophagia. A few large accumulations of lymphocytes.

*Hypothalamus, posterior part of the mammillary body:* As the preceding; in addition, a good many microglia cells.

*Medulla oblongata, corresponding to coll. fac.:* Marked perivascular infiltration with lymphocytes. Abducens nucleus normal. The nerve-cells of the facialis nucleus have undergone either neuronophagia or moderate degeneration. The lateral part of the section shows diffuse cellular degeneration, oedema and lymphocytic infiltration. Anteriorly there is merely a slight oedema.

*Medulla oblongata, corresponding to the tip of the 4<sup>th</sup> ventricle:* Pronounced inflammatory changes with acute swelling of some of the nerve-cells, in particular laterally to the hypoglossal nucleus, the cells of which show merely a moderate oedema. The olive appears normal.

*Cervical cord:* Marked oedema; here and there, perivascular infiltration with lymphocytes in the white substance. Accumulations of lymphocytes in the anterior horns, neuronophagia of the majority of the nerve-cells, and infiltration with microglia cells. In the posterior and lateral horns, similar changes though less pronounced.

#### *Case 13 (B. J.).*

Postural reflex examination on the 4<sup>th</sup> day of illness. Temperature 38.8°. Pulse 118. — At that time the patient was very ill, hazy and slightly cyanotic. The right abducens nerve was paralyzed, and the deglutition was completely paralyzed; the mouth was continuously full of saliva. The right pupil was larger than the left. Diffuse impairment of the muscular power in all groups of muscles. Respiration weak, but regular. No paralysis of the bladder.

The outcome of the examination was not quite definite, as there was no rise in the blood pressure, but a slight rise in the pulse rate. This result will be discussed later in connection with the findings in Case 12.

The patient was getting worse rapidly and died a few hours after the examination, with increasing cyanosis and steadily increasing impairment of the heart function.

*Abstract from the Autopsy Record (Histol. 21971):*

*Hypothalamus, corresponding to the optic chiasma:* Hyperemia and perivascular oedema, but only a few accumulations of lymphocytes and microglia cells. Several nerve-cells show degenerative changes.

*Hypothalamus, corresponding to the anterior part of the mammillary body:* Same features as above. Besides, near the 3<sup>d</sup> ventricle, accumulations of lymphocytes and microglia cells, together with neuronophagia of nerve-cells.

*Hypothalamus, corresponding to the posterior part of the mammillary body:* Degenerative changes in some of the nerve-cells.

*Medulla oblongata, corresponding to coll. fac.:* Posteriorly, marked infiltration of lymphocytes. Acute swelling of the nerve-cells in the facialis nucleus; here and there, pronounced hyperemia and perivascular infiltration with lymphocytes.

*Medulla oblongata, corresponding to striæ med.:* Same features as in the preceding section, only that the lymphocytic infiltration here is more pronounced.

*Medulla oblongata, corresponding to the tip of the 4<sup>th</sup> ventricle:* The hypoglossal nucleus is well preserved. Laterally hereto, involving also the nucleus ambiguus, the nerve-cells show pronounced acute swelling, oedema and lymphocytic infiltration.

*Cervical cord:* Here and there, perivascular lymphocytic infiltrations in the white substance. The anterior horns show pronounced oedema, hyperemia and lymphocytic infiltration; and all the nerve-cells have undergone degenerative changes or neuronophagia.

*Lumbar cord:* Same features as in the preceding section, only a little less pronounced.

*Case 14. (B. A.).*

Postural reflex examination on the 4<sup>th</sup> day of illness. Temperature 37.6°. Pulse 108. — There was a pronounced, diffuse impairment of the muscular power, the patient being able to move the extremities but little. Total paralysis of the thoracic abdominal and cervical musculature. The patient was lying in respirator. There was no paralysis of the bladder or intestine.

The examination showed abnormal postural reflexes: a rise of 10 mm. in the blood pressure, but practically no change in the pulse rate.

On the 6<sup>th</sup> day of illness, the patient got worse. She became more and more hazy and had difficulty in speaking; and she died on this day. At no time was there any paralysis of the bladder or intestine.

In two cases with high fever and, consequently, maximal peripheral vasodilatation and high skin temperature, an indirect chilling test was performed (Cases 4 and 12). Both of these patients showed no fall in the skin temperature, but, considering the abnormal initial values, it would hardly be warrantable to attach any particular significance to the outcome of these two tests.

As to the postural reflex examinations, it will be appropriate at once to emphasize a fact that makes it difficult to interpret the results obtained. Kopp (1939) has shown that examination of patients with artificial fever by tipping them with the legs downwards often gives abnormal results, *i. e.*, a fall in blood pressure. If the converse be the case, that is, if a fever by itself might imply a tendency to a rise in blood pressure on tipping of the body with the head down, has not been ascertained. An explanation of the fall in blood pressure on tilting of the body with the legs down, in a state of fever, is not given in the studies reported by Kopp. Probably this phenomenon may be attributable to the reduction in the «effective blood volume» which presumably takes place on the stagnation of the blood in the dilated capillaries in fever. The amount of blood given off to the lower extremities will thus be relatively greater and more easily able to bring about a break in the regulation, giving a fall in blood pressure.

If this explanation be correct, however, one would not a priori expect that a rise in blood pressure would appear more readily on tipping of the body with the head down in fever, in which condition the lowered «effective blood volume» can only give a smaller rise in the venous pressure than normally. But, even though it thus seems improbable that the fever in itself may be responsible for the occasional abnormal results in the tests here presented, the conditions mentioned call for a certain degree of reservation in the final estimation of the significance of the obtained results.

In 4 patients the tests showed a normal reaction, the blood pressure keeping unchanged while the pulse rate was falling or unchanged on tipping of the body with the head down. All these 4 patients survived the illness, which was severe in 3 of them. It is to be mentioned that one of them, Case 4, was examined in fever. The remaining 5 patients showed an abnormal reaction. They all died of poliomyelitis. Most of them had fever at the time of the examination. Cases 10 and 11, and in a lesser degree, Case 14,

showed a typical failure of the regulatory mechanism. In Cases 10 and 11 there was a considerable rise in blood pressure, notwithstanding the fall in pulse rate. In Case 11 the abnormality was further verified by a test with tipping of the body with the legs down. In Case 14 there was a barely demonstrable rise in blood pressure and no definite change in the pulse rate. The outcome of the test in Case 10 and 11 shows that there is no definite demonstrable defect in one of the compensations that normally has to take place: the decrease in the pulse rate. It seems most likely that the rise in blood pressure, in spite of the considerable fall in pulse rate is ascribable to a failure of the vasodilatation, which presumably takes place normally simultaneously with the decrease in pulse rate. This vasodilatation has not been demonstrated, it is true, but the assumption of its occurrence finds support in the present results.

In Cases 12 and 13 we meet with another abnormality: The blood pressure remained unchanged but the pulse rate increased. It is difficult to give any adequate explanation of this peculiar result, which resembles a Bainbridge reflex.

On comparison of the results obtained with the two methods of examination, one has the impression that the vascular regulation due to the shift in the blood volume is effectuated more readily than the heating effect, or that the shifting of the blood volume is a stronger stimulus. From the cases in which both tests were performed it is evident that the postural reflex test has given normal results even in cases where a defect in the autonomic regulation could be demonstrated by means of the indirect heating test. Besides, the postural reflex tests have given abnormal results only in the most severe cases of the disease, which all terminated fatally. — That the difference in the results obtained with the two methods is not due to the regulation on the change in posture being brought about chiefly by a change in the pulse rate, has been mentioned before, and it is also plainly evident from the results recorded in Table 1.

The histological examination in the fatal cases has demonstrated the presence of extensive pathological processes in the medulla oblongata and hypothalamus. These changes have been of such a character and localization that they may readily explain the abnormalities of the blood pressure and heat regulation. It is only

reasonable to assume that the vasomotor centers in the floor of the 4<sup>th</sup> ventricle and the centers for heat regulation, which are located in the hypothalamus — and perhaps in the medulla oblongata, too (Magoun, 1939) — have been affected in the cases here examined. Also the respiratory center, which is taken to be located in the reticular formation of the medulla oblongata at the level of the inferior olivary nucleus (Pitts, Magoun & Ranson, 1939), may be damaged readily in such a degree as to give serious consequences; for all the specimens here examined showed pathological changes laterally to the hypoglossal nucleus. In one case (10) the terminal symptoms were suggestive of an acute damage to the respiratory regulation.

The pathological findings in the medulla oblongata and superior parts of the central nervous system show merely, however, that the demonstrated autonomic abnormalities may have been localized to these parts of the nervous system, and probably have been so partially. But, as such changes are seen also in the lateral horns of the medulla oblongata and in the sympathetic chains, it is not possible to decide how great a rôle the damage to the individual sectors of the regulatory system may have played in the individual cases.

### Summary.

By indirect heating tests and by postural reflex examination the writer has tried to demonstrate the presence of autonomic abnormalities in the acute phase of poliomyelitis.

In severe cases of poliomyelitis the indirect heating test revealed a failure of the skin temperature to rise on the extremity examined.

Cases of moderate severity showed various degrees of abnormality of the temperature curve, and in the mildest cases the reaction was normal.

In the cases showing an abnormal reaction the test was repeated after the first acute stage of the disease had passed. The second test gave a normal skin temperature curve in every instance.

Postural reflex examinations showed a normal reaction in several cases, and these patients survived. Other, more severe, cases showed abnormalities in the form of a rise in blood pressure on tipping of the body with the head down or a reaction reminding of the Bainbridge reflex; and all these patients died.

The histological examination carried out in the fatal cases has demonstrated pronounced changes in the medulla oblongata and hypothalamus that may very well have been responsible for the demonstrated abnormalities. But, it is pointed out that pathological processes in the lower parts of the autonomic nervous system probably play just as great a rôle, if not greater.

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## Measurements of the specific Resistance of the human Body to direct Current.

By

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### 1. Introduction.

Many investigators have tried to measure the resistance of the human body (1). But, as this is a threedimensional conductor of complicated shape, the resistance is not a property of the body itself, but depends on the shape and the dimensions of the electrodes used. The well-known formula:

$$R = \frac{l}{d} \varrho, \text{ — — — — — (I)}$$

connecting the resistance  $R$ , the specific resistance  $\varrho$ , the length  $l$  and the cross-section  $d$  is only valuable for a cylindrical conductor and does not hold for the total human body, with its complicated shape.

A quantity of much more importance than the »resistance of the body» is its specific resistance. This is a material-constant, which is a function of the place within the body, as it will be different for different tissues. It plays a part in a number of cases e. g.: the conduction of a current through the body of a person stricken by an electric accident, the heat-development in the body, caused by an electric current and the flowing of electricity through the body, caused by muscular contraction e. g. of the heart.



Furthermore the resistance, as it is measured with given electrodes, has to be located for the greater part in the skin. The contribution of the skin to the total resistance depends highly on its watercontents, and thus its resistance is irregularly variable with outer circumstances. Yet in many cases the skin has been the object of the measurements.

We have taken up the problem to measure the specific resistance of different parts of the live human body. Measurements on cadavers have the disadvantage, that the quantity to be measured may change after death and that it is impossible to study the influence of the conditions of the body (see p. 604).

The difficulty of the measurement of the specific resistance of the live body is a consequence of the fact that we cannot cut from it a piece of a simple geometrical shape and of the badly conducting skin, enveloping the tissues to be investigated. How these difficulties may be encountered, will be described furtheron.

As is well known, the human body is an electrolytical conductor. So polarization phenomena are to be expected and are indeed often stated. (2) The common method to prevent polarization is the use of alternating current. This, however, may involve other complications, the human or animal tissue having a specific resistance, depending on the frequency of the current (2). Therefore we have used direct current as the simplest case, but further as it is our intention to apply our results to the action-current of the heart. The frequencies, which occur in electrocardiography are small and the specific resistance of our tissues for this frequency will be very near the value, we have found with direct current i. e. with a frequency zero.

## 2. Method of measurement.

To begin with, we will treat the simple case of a nearly homogeneous cylindrical part of the human body e. g. a part of the arm.

In fig. 1. the principle of the electrical measurement is illustrated. A current  $i$ , given by a battery B, passes through the cylindrical conductor A (e. g. the arm). Near the electrodes  $C_1$  and  $C_2$  (the current-electrodes) the current is not homogeneous over the cross-section of the cylinder, but at some distance it is. From the poten-

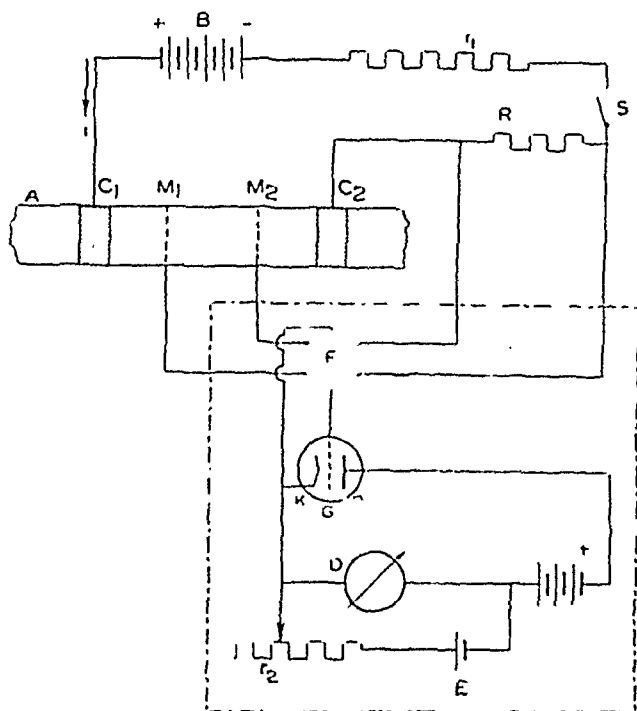


Fig. 1. Wiring-diagram for the measurement of the resistance of a part of the cylindrical conductor between the measuring-electrodes  $M_1$  and  $M_2$ . The current  $i$  originated by the battery  $B$ , is regulated by the large resistance  $R$ . The p. d. between the measuring-electrodes  $M_1$  and  $M_2$  is determined by the triode-voltmeter, designed in the dotted frame, as is described in the text.

tial difference  $V_1 - V_2$  between the cross-sections  $M_1$  and  $M_2$ , chosen between  $C_1$  and  $C_2$ , the resistance  $R$  of the cylindrical part  $M_1M_2$  is deduced with Ohm's law:

$$R = \frac{V_1 - V_2}{i} \quad \text{----- (II)}$$

The specific resistance  $\rho$  of this part of the body is computed from the resistance  $R$ , the distance  $l$  of  $M_1$  and  $M_2$  and the cross-section  $d$  of the cylinder, according to formula (I).

The potential difference  $V_1 - V_2$  between  $M_1$  and  $M_2$  must be measured in such a way, that no current passes through the measuring instrument connected to the electrodes applied in  $M_1$  and  $M_2$  (the measuring-electrodes). Then the resistance of the skin is put out of the way. This is seen from fig. 2. If a current should pass in the direction of the arrow from the tissue to an electrode ( $M_1$  or  $M_2$ ), the potential of the tissue immediately under the skin would be higher than the potential of the electrode and the reverse. But

if the the current is zero, the p. d. between the tissue and electrode is also zero, how large the skin's resistance may be. So it is possible to measure the p. d. between two points inside the tissue below  $M_1$  and  $M_2$  which equals the p. d. of the electrodes  $M_1$  and  $M_2$  themselves (fig. 1).

Further there will be no disturbing polarization at the electrodes. As for the measuring-electrodes  $M_1$  and  $M_2$  it is absent, for polarization is a consequence of a current passing from the electrode to the electrolyte or the reverse. The polarization at the current-electrodes  $C_1$  and  $C_2$  does not enter into the equation (II), as it occurs outside

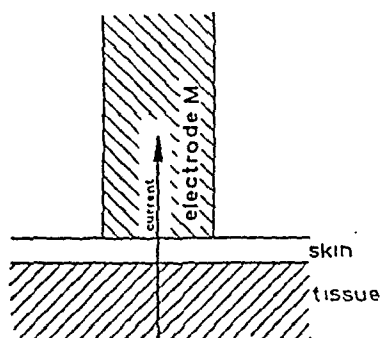


Fig. 2, A current from tissue to electrode causes a p. d. between both.

the electrolyte  $M_1M_2$  with electrodes  $M_1$  and  $M_2$ , to which it is applied. An interior polarization, caused by changes of concentration of the electrolytes in the cells as a consequence of the current is not eliminated in this way. It may have an influence on the value of the specific resistance found with direct current.

The measurement of a p. d. without current passing is a well known physical problem. The method, that we have used, is to be found in the dotted frame of fig. 1. The electrodes  $M_1$  and  $M_2$  are connected to the grid  $G$  and the cathode  $K$  of a three-electrode valve respectively. A negative grid-potential suppresses the grid-current, so that the current through the electrodes  $M_1$  and  $M_2$  is indeed zero. The changes of the anode-current of the valve are measured with the galvanometer  $D$ . But as the changes are much smaller than the anode-current itself, the main value of this current is compensated by the current of an accumulator  $E$ , regulated by a resistance  $r_2$ . Only the changes in the anode-current are indicated by the galvanometer  $D$ .

Such a change is caused by closing with a switch  $S$  the current  $i$  through the cylinder to be investigated. The potential difference  $V_1 - V_2$  between  $M_1$  and  $M_2$  which is zero for  $i = 0$ , now acquires the value:

$$V_1 - V_2 = iR \text{ [see formula (II)]}$$

The change  $V_1 - V_2$  of the grid-potential, roused in this way, gives a deflection of the galvanometer.

It is not necessary to have the instrument callibrated. It is much simpler to insert a resistance  $R'$  in the main circuit and to measure the potential difference  $iR'$  between its terminals with the device described above. A six-polar switch  $F$  allows the connection of grid and kathode of the valve to the measuring-electrodes  $M_1$  and  $M_2$  or to the terminals of  $R'$ . If the deflection of the galvanometer  $D$  is proportional to the p. d. applied to the valve, the ratio of the deflections with the two connections mentioned is equal to the ratio of the potential differences  $iR$  and  $iR'$  and thus of the resistances  $R$  and  $R'$ . As  $R'$  is known,  $R$  is found in this way.

The value of  $i$  needs no be accurately measured. The only condition is, that the current, flowing through  $M_1M_2$  and  $R'$  is the same. So during the measurement the current should not fluctuate. In order to prevent fluctuations caused by changes in contact of the electrodes  $C_1$  and  $C_2$  with the body, a large resistance  $r_1$  is inserted in the main circuit. In the larger number of our experiments we used a resistance  $r_1$  of one or two  $M\Omega$  in connection with a battery  $B$  of 90 Volt.

In the former is said, that the resistance of the skin may have any value, how large it may be. But if this resistance is too large, the measurement will be effectuated by disturbances caused by inevitable leakage. This leakage may occur either in the measuring apparatus itself or over the skin. To make this error as small as possible the skin's resistance must be reduced, to which purpose we have used wet electrodes  $M_1$  and  $M_2$ . As such little cushions, filled with wet cotton-wool were used, or small carbon rods with a drop of water at the end<sup>1</sup>. A small conductance through a layer of dirt or sweat on the skin gives large errors. Therefore the skin is thoroughly cleaned and dried before each measurement. Under bad conditions

<sup>1</sup> Wetting of the electrodes with a salt solution gives difficulties, which we will not discuss.

(wet weather) the disturbances caused by leakage may be troublesome. The resistance of the skin has then to be reduced appreciably. This is done by piercing it with a snapper. The wet electrode is applied on the drop of blood.

The measuring-electrodes  $M_1$  and  $M_2$  as a rule will have a p. d. with the skin. This two p. d.'s are not exactly equal and therefore the p. d. between  $M_1$  and  $M_2$  is not zero, when no current  $i$  passes through the conductor  $M_1M_2$ . This disturbing effect does not give an essential difficulty, as the potential difference  $V_1 - V_2 = Ri$  is superposed on the p. d. mentioned above. But, as the latter is often inconstant, the zeropoint of the galvanometer is gradually shifting. This may make an accurate measurement difficult.

If the above mentioned disturbing p. d. is rather large, the anode current of the three-electrode valve is changed appreciably. The grid-bias is changed by that, which involves an error. Therefore the negative grid-potential can be regulated, to adjust the anode-current before each measurement to the same value.

When the resistance of a part  $M_1M_2$  of a cylindrical conductor is measured according to the method described, the equation (I) gives the specific resistance  $\rho$ . If the conductor is not homogenous the result of the computation of  $\rho$  from (I) is the mean value of the specific resistance.

### 3. Tests.

Before we mention the results of our measurements, we will discuss some tests, which may increase their trustworthiness.

To test the electrical equipment we have replaced the part  $M_1M_2$  of the human body by a metallic resistance of about  $100 \Omega$ . Two large resistances of about one  $M\Omega$  take the place of the skin at the two measuring electrodes  $M_1$  and  $M_2$ . On some days the value found for the metallic resistance was erroneous. Then the table, on which the equipment was installed, was heated till the apparatus worked well and could be used. We may speak only then of a resistance if there is a proportionality between p. d. and current intensity (Ohm's Law). As sometimes this proportionality is denied for the human body, we have tested it with our method. The current  $i$  through the arm was varied between 0.08 and 0.85 m A and the p. d. between two points on the arm was measured. Fig. 3 shows that in

this current-interval Ohm's law is valid and so a resistance does exist.<sup>1</sup>

The p. d. between two points on a cylindrical conductor e. g. on the arm, lying on the same straight line parallel to the axis of the arm, must be proportional to their distance  $l$  [see equation (1)]. The experiment with measuring-electrodes on distances between 0.5 and 10 cm, placed on the arm, shows that this proportionality exists within the limits to be expected. If the distance  $l$  of the measuring-electrodes is too large, it does not hold, as then the cross-

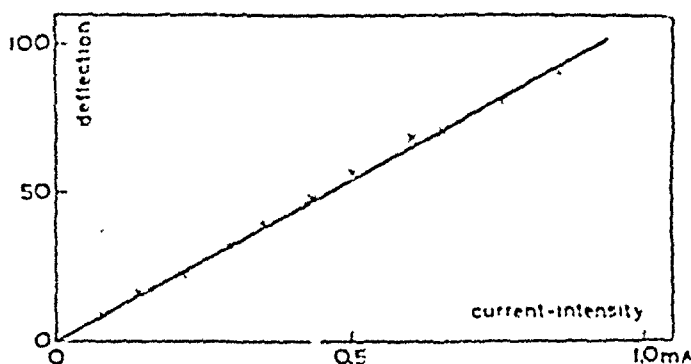


Fig. 3. The deflection of the galvanometer, that is proportional to the p. d. between two points on the skin, appears to be proportional to the current intensity i. e. Ohm's Law is valid for the live human tissue.

section of the arm and the properties of the tissue are no longer constant along  $l$ . With small distances the dimensions of the electrodes may play a part. In this case the electrodes must have a small diameter, which is only a fraction of their distance.

Previously (p. 588) we have mentioned, that we have pierced the skin with a snapper to reduce its resistance. In a special series of measurements we have stated that, under tolerable conditions, there is no systematic difference between the resistance found with the intact skin and with the pierced skin. In the second case however the mean error of the measurement is much smaller. So we may use the method with the intact skin with the certainty, that it gives in the mean the same value of the resistance, as would be found with a direct contact with the well-conducting tissue.

<sup>1</sup> If a «resistance» of a part of the body is measured in which the skin is included, the current increases more rapidly than the p. d. This is a consequence of a piercing of the skin at higher tension (Freiberger l. c.)

A last test concerns the vectorial character of the intensity of the electric field at the surface of the body, through which a current flows. This electric field  $E$  is related to the potential difference  $V_1 - V_2$  between two points 1 and 2 (fig. 4) in such a way that:

$$V_1 - V_2 = l E \cos \varphi \quad \text{--- (III)}$$

In order to test this relation we have measured the p. d. between two electrodes 1 and 2 having a fixed distance  $l$  and being placed on the skin of the arm. The current  $i$  through the arm was kept constant. The direction of  $l$  was varied; the place of  $l$  (or more exactly the place of the point halfway 1 and 2) was kept fixed. The potential difference  $V_1 - V_2$  between 1 and 2, plotted as a function of  $\varphi$  gave a sinusoid, as is to be expected from equation (III).

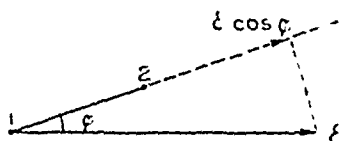


Fig. 4. Vectorial character of the electric field  $E$  on the surface of the arm. The p. d. between two points 1 and 2 is proportional to the cosine of the angle  $\varphi$  between the line joining 1 and 2 and the direction of the field  $E$ .

To get an idea of the errors involved in the measurement of the resistance  $R$  of a part of the body, the resistance of a part of the arm of two persons was measured repeatedly on different days, the skin remaining intact. The mean error was about 3 %.

It must be remarked, that the error in the determination of the specific resistance is larger, for this quantity must be evaluated from the resistance, the cross-section and the length of a part of the arm. The errors of the last two quantities make the value of the specific resistance less accurate than that of the resistance. The error of the specific resistance may be estimated to be about 6 %.

#### 4. Method of the inhomogeneous current-distribution.

In all non-cylindrical conductors a homogeneous current-distribution (i. e. a state in which the current-density is the same in the whole volume and has the same direction everywhere) cannot be realized. For a cylinder not only a homogeneous but also an inhomogeneous current-distribution may reveal interesting facts. There-

fore we have studied the case in which the current enters and leaves the part of the body to be investigated by two electrodes, each making contact with the skin in a small spot of a few millimeters diameter. The investigation of the p.d. on the skin around these electrodes (current-electrodes) gives the possibility of evaluating the specific resistance of the tissue under the skin.

To investigate the arm with the above-mentioned method, we have used a system of four electrodes, sliding along a bar of insulating material. Each electrode consists of a well insulated carbon rod of a diameter of a few mm at the end. This is so small, that it may be neglected with respect to the distances of the electrodes. The four electrodes are adjusted on a straight line and on the desired distances. The outer pair is used as current-electrodes and the inner

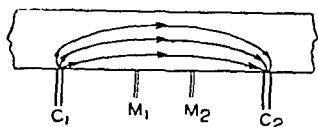


Fig. 5. Lines of flow of the current through a cylinder in the case of an inhomogeneous current-distribution.

$C_1$  and  $C_2$  = current-electrodes.

$M_1$  and  $M_2$  = measuring-electrodes.

pair as measuring-electrodes (the p. d. of which is measured). We have always placed the measuring-electrodes  $M_1$  and  $M_2$  symmetrically with respect to the current-electrodes  $C_1$  and  $C_2$ , in such a way that the point halfway the first ones is also halfway the second ones (fig. 5). Now a current  $i$  is sent through the cylindrical conductor (e. g. the arm) from one current-electrode ( $C_1$ ) to the other ( $C_2$ ). The lines of flow of the current are curved, diverging and converging at  $C_1$  and  $C_2$  respectively. The potential difference  $V_{M_1} - V_{M_2}$  between the measuring-electrodes  $M_1$  and  $M_2$  is determined after the method previously described. It is proportional to the current-intensity  $i$ , as Ohm's Law holds good for the tissue. So:

$$V_{M_1} - V_{M_2} = i R_{C_1 M_1 M_2 C_2} \quad \text{--- --- --- (IV)}$$

We will call  $R_{C_1 M_1 M_2 C_2}$  the »resistance», though it is not a proper resistance, but a proportionality-factor, that has the dimension of a resistance. It depends on the shape of the conductor (e. g. a cylinder) and the position of the electrodes and is proportional to the specific resistance of the tissue.



If the conductor is a cylinder or a sphere, and if the specific resistance is constant throughout its volume, the distribution of the current and thus  $R_{C_1M_1M_2C_2}$  can be computed.

The problem of the current in a sphere, the current-electrodes being point-shaped, is rather simple and the value of the »resistance» is expressed in a closed formula. But in the case of a cylinder we are lead to rather tedious numerical calculations, the result of which we have laid down in a table. We will not discuss these calculations, because they may be only interesting to the mathematically schooled reader.

To secure the correctness of the reckoning in the case of a cylinder, we have used a model. In the wall of a glass cylinder four platinum wires are molten in, lying in a straight line, parallel to the axis of the cylinder. The cylinder is filled with an electrolyte (a solution of NaCl) of known specific resistance. A direct current is sent through the electrolyte, using the two outer electrodes as current-electrodes and the p. d. of the two inner electrodes (measuring-electrodes) is measured. It was in good agreement with the value, predicted mathematically, and thus we may trust our calculation.

## 5. Results of the measurements.

### A. *Homogeneous current-distribution in cylindrical parts.*

In the first place we have examined the arm. It rests horizontally on a support, with the back of the hand upward. The current is passing from hand to hand, to secure a homogeneous current-distribution. The specific resistance is deduced as a rule from the p. d. of points on the dorsal side of the arm and on a distance of 5 cm from each other. So the mean specific resistance of a part of the arm, 5 cm long, is found in a point halfway between the two measuring-electrodes.

The surface of the cross-section of the arm is determined from its circumference. This is measured with a piece of cord, wound some times around the arm. A correction accounts for the thickness of the cord and for the slight »ellipticity» of the arms cross-section.

The specific resistance thus found depends upon the place i. e. on the distance from the hand or from the shoulder. To define the place we have measured, along the stretched arm, the distance from the wrist. (proc. styloideus ulnae).

Besides this, the value of the specific resistance depends on the attitude of the arm, on the test-person and on unknown circumstances.

Fig. 6. gives a curve, illustrating the way in which the specific resistance of the arm depends upon the place. The average value for the fore-arm amounts to about  $230 \Omega \text{ cm}$ , corresponding to a solution of NaCl of only 0.2 %. It is remarkable that Rosenthal (2) finds about the same value using a. e. of 2000 cycles. The place of the elbow-joint is by no means marked on our curve. So there is no additional resistance in this joint, as is sometimes asserted.

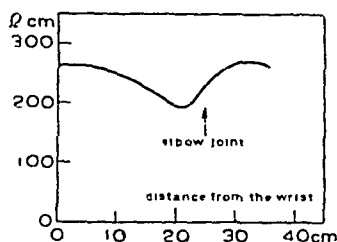


Fig. 6. Specific resistance of the arm as a function of the distance from the wrist.

It would be interesting to explain the shape of the curve of fig. 6. We expected first, that the badly conducting bones might be the cause of the differences of the mean specific resistance in different parts of the arm. We therefore have measured the diameter of the bone with a Röntgen-apparatus on different places of the arm. We hoped to be able to compute from these data the specific resistance of bone and flesh separately. This, however, appeared to be impossible as the mean specific resistance can be larger in parts of the arm with relatively less of the badly conducting bone and the specific resistance of the bone even can come out negative. We therefore cannot give an explanation of the curve of fig. 6.

The supposition of the homogeneously conducting arm is too simple. This appears not only from the different values of the specific resistance along the arm as mentioned above, but also from the fact, that the lines of equal potential, that can be drawn on the surface of an arm through which a current flows, are not situated in a plane perpendicular to the arm. We could state this in the following way. One measuring-electrode got a fixed place on the arm. The other measuring-electrode was placed such, that the p. d.

between both electrodes was zero. Different positions of this other electrode around the arm fulfill this requirement. The line joining these positions can be drawn on the skin and is a line of equal potential as mentioned above. It is difficult to determine these equipotential lines with accuracy, as a slight change in the attitude of the arm seems to have an appreciable influence on them. We therefore have not constructed the whole equipotential line, but measured the distances of four of its points on the medial, lateral, dorsal and ventral sides of the arm from the top of the middle-finger. For points about halfway the fore-arm the following is found. In the average the equipotential line is on the medial side about 2.5 cm further from this top than on the lateral side. The obliqueness of the plane in which the equipotential line is situated follows from this result to be about  $15^\circ$ . It indicates that less-conducting tissue is situated between the place of the oblique equipotential line and the elbow at the medial side or between this place and the wrist at the lateral side. A sketch of the course of the lines of flow of the current may elucidate this, but we will not insist on this.

The electrical inhomogeneity of the arm appears also from measurements of the p. d. between two measuring-electrodes at 5 cm distance placed at the lateral, medial, ventral and dorsal side of the arm, each time at the same distance of the wrist. The p. d.'s found in this way are somewhat different. So the value of the specific resistance given by fig. 6 cannot be quite exact, as it is derived from measurements at the dorsal side of the arm only. The mean value along the whole fore-arm, however, will not be affected to an appreciable extent by the inhomogeneity.

The fingers are examined with a current entering at the top of the finger and leaving at the other end. We have only measured a mean value of the specific resistance over nearly the whole length of the finger. The cross-section is found from the circumference as in the case of the arm. There is no appreciable difference in the specific resistance of the different fingers. The mean value is  $235 \Omega$  cm. It is remarkable that the fingers, notwithstanding the larger bone-contents, have the same specific resistance as the arm.

The middle hand can in first approximation be considered as a rectangular plate of uniform thickness and so formula (I) may be applied. The current is entering at the four fingers and leaving

at the wrist. The mean specific resistance is found to be about  $280 \Omega \text{ cm}$ .

The neck is an approximately cylindrical part of the body with relatively little bone. It is investigated by means of a current, sent from the head to the arm i. e. to the trunk. Although the neck is no quite a cylinder, yet in the thinnest part the lines of flow will be nearly parallel. So, by measuring the p. d. between two electrodes at some centimeters distance, it is possible to find a rather reliable value of the specific resistance. The value thus found is  $280 \Omega \text{ cm}$ .

Finally we will mention our measurements on the trunk. To secure a homogeneous current-distribution the current is conveyed at the upper side by head and arms and at the lower side by the legs. By large resistances in the three branches at the upper side and in the two at the lower side the current is distributed equally, the relatively small resistance of the skin at the points of entrance of the current being of little influence. So the lines of flow of the electricity are nearly parallel inside the trunk. Indeed the p. d. between the measuring-electrodes is zero, if the line joining them is perpendicular to the axis of the trunk. The distance of the measuring-electrodes varied between 2 and 12 cm. They were placed one above the other, the line joining them being parallel to the axis of the trunk. The mean specific resistance is found to be about  $415 \Omega \text{ cm}$ .

This value is large as compared with the above mentioned one's. This may be partly attributed to the air in the lungs, which is a non-conductor. To confirm this statement the mean specific resistance is measured with maximal filled and with minimal filled lungs both. Indeed the specific resistance in the first case ( $455 \Omega \text{ cm}$ ) is larger than in the second one ( $375 \Omega \text{ cm}$ ), as was to be expected from the larger (resp. smaller) air-contents of the trunk.

Even in the second case the lungs still contain some air, which enlarges the mean specific resistance of the trunk. Could this be removed, the value  $375 \Omega \text{ cm}$  would still be diminished a little, say by about one third of the difference  $455 \Omega \text{ cm} - 375 \Omega \text{ cm}$ , as the residual air is about one third of the vital capacity. So the trunk, deprived of air, would have a mean specific resistance of  $375 - 25 = 350 \Omega \text{ cm}$ . This is much larger than is found for the

computed, according to the above considerations, the specific resistance of the head. We will only discuss the results.

In the first place we have investigated the p. d. between the measuring-electrodes, when the current-electrodes were placed at points of the head lying diametrically opposite (near the temples). According to the supposition of the homogeneous head, i. e. of the well conducting bone, the apparent specific resistance is  $840 \Omega$  cm. This large value points to the large specific resistance of the bone of the skull, which hinders the current to enter into the brain. The value found with the second hypothesis (of the isolating skull) is  $70 \Omega$  cm. This is much smaller than can be expected for normal human tissue, indicating that this hypothesis too must be rejected; a part of the current does enter into the brain.

We have also measured the apparent specific resistance, placing the current-electrodes on distances, smaller than a half-circumference. The measuring-electrodes are symmetrically placed on the same great circle as the current-electrodes. The point halfway the electrodes was the centre of the fore-head. This method has the advantage that the departing from sphericity of the head is smaller in the smaller part which is investigated. In this case too, the apparent specific resistance is smaller according the second hypothesis (of the isolating skull). It is very remarkable that the values found are depending on the distance of the electrodes and approach to the value of  $230 \Omega$  cm, characteristic for human tissue, when the distance of the current-electrodes approaches to zero. This is to be expected, as with a small distance of the electrodes, the lines of flow of the current will take their course through the conducting layer outside the skull, without being influenced appreciably by it. If this distance could be made smaller than the thickness of this layer, the current would not be influenced at all by the skull, and both hypotheses would give the same value, that of the tissue of the layer. In fig. 7 the points give each the average of several measurements with one and the same distance of the current-electrodes and with different distances of the measuring electrodes. All points refer to the same test-person. The great circle on which the electrodes are situated is horizontal, but in a few cases we have measured the apparent specific resistance in placing the electrodes on a vertical circle and have found nearly the same value.

From fig. 7 it is seen that the apparent specific resistance,

according to the hypothesis of the isolating skull, does not depend very strongly on the distance of the electrodes and is not very far from the normal value. So the hypothesis of the isolating skull is nearer to the truth than that of the homogeneous sphere i. e. the bone conducts so badly that only a small part of the current enters into it. This part is the greater, the larger is the distance of the current-electrodes.

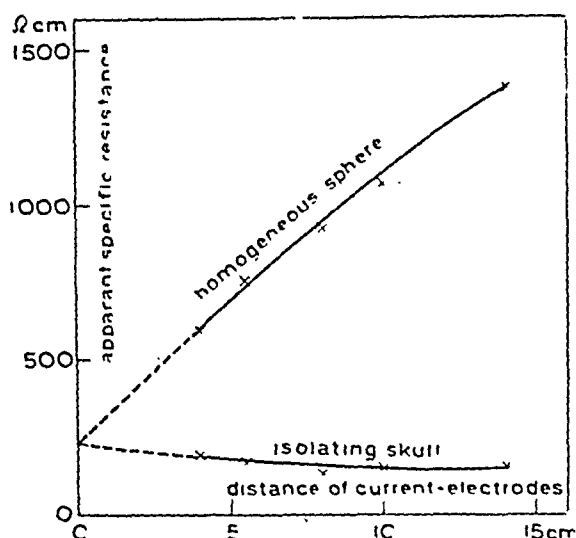


Fig. 7. Apparent specific resistance of the head as a function of the distance of the current-electrodes. Difference of the result according to the hypothesis of the homogeneous sphere and to that of the isolating skull.

That the values of the apparent specific resistance, found with current-electrodes placed diametrically on the head, are so small with respect to the one's, given in fig. 7, so that they do not fit at all in the curves, must be a consequence of the small thickness of the temples. The isolating layer there is so thin that the current enters for a large part into the brain through the temples and the current is not so much concentrated on the fore-head.

### C. Inhomogeneous current-distribution in the arm.

In this case the four electrodes are placed on a straight line on the fore-arm, parallel to its axis. The position of the arm is the same as described on p. 593; the electrodes are placed as a rule on its upper-side i. e. on the dorsal side. The electrodes are arranged symmetrically, just as in the case of the investigation of the head,

the point halfway the measuring electrodes being halfway the current-electrodes.

A series of measurements is made with different distances of both current- and measuring-electrodes. The point halfway, mentioned above, however, is the same for the whole series. The specific resistance found in this way appeared to be not invariable, but varies with both distances, principally with the distance of the current-electrodes. Therefore we have taken the mean value for different distances of the measuring-electrodes and plotted it against their common distance of the current-electrodes. From fig. 8

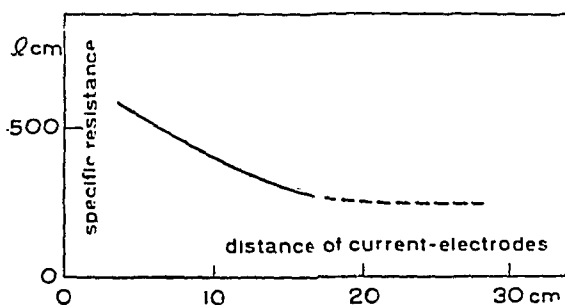


Fig. 8. Apparent specific resistance of the arm as a function of the distance of the current-electrodes.

we read the remarkable fact, that the specific resistance is found the smaller, the larger is the distance of the current-electrodes. It approaches a value of about 240  $\Omega$  cm, (as is found previously for homogeneous current-distribution) if the distance of the current-electrodes becomes large enough. The curve of fig. 8 is found as a mean from different series of measurements for two test-persons.

So our hypothesis of the homogeneous and isotropic tissue of the arm has to be rejected. A possible explanation of the fact illustrated by fig. 8, were the influence of the badly conducting layer of tissue e. g. of fat, surrounding the better conducting muscular tissue. Just as in the case of the head it is easily seen without reckoning (and can be confirmed by calculation) that the current is forced to enter the deeper layers, if the current-electrodes are farther apart. If the distance is large enough, the specific resistance of these deeper layers is found. But if the distance of the current-electrodes is small, the current flows for the larger part in the more superficial layer of fat, with its higher specific resistance. So the specific resistance

found from the measurement is the greater, the smaller is the distance of the current-electrodes. This fact is illustrated by fig. 8, in which the value of the apparent specific resistance is plotted as a function of the distance of the current electrodes. The curve connecting the experimental points (full line) can be extrapolated (dotted line) to the value of about  $240 \Omega \text{ cm}$ , found with a current flowing through the arm in the direction of its axis. This value would be found with a sufficiently large distance of the current-electrodes.

## 6. Anisotropy of the muscular tissue.

Another explanation of the fore-going peculiarity may be a possible electrical anisotropy of the muscles of the arm. These consist of long fibres, arranged nearly parallel. A current flowing in the direction of these fibres i. e. parallel to the axis of the arm, encounters a resistance which is not very far from the true resistance of the contents of the muscular fibres. But a current, flowing perpendicularly to the direction of the fibres, encounters a larger number of cell-membranes on the same length of path and therefore the specific resistance will be larger.

To test this supposition by experiment, we must study a case in which the current flows as much as possible perpendicularly to the direction of the muscular-fibres i. e. perpendicularly to the axis of the arm. An exact realisation of these transverse current is not possible without cutting a cylindrical piece of muscular substance of the correct orientation out of a muscle. An investigation on a live arm can use a field of flow as is generated by two current-electrodes  $C_1$  and  $C_2$ , situated in the same perpendicular cross-section of the arm and in opposite points. As is shown in fig. 9 in a section in length, the lines of flow will then have a course which is on the whole about perpendicular to the axis of the arm. However, in the neighbourhood of the current electrodes  $C_1$  and  $C_2$  the lines of flow are not at all perpendicular to the axis of the arm.

The solution of the mathematical problem of the current in an anisotropic cylinder, having an uni-axial symmetry of its electric conductivity, the axis of minimal specific resistance coinciding with the axis of the cylinder, can easily be deduced from the solution of the problem of the isotropic cylinder. As formerly we will not give



the mathematical deduction, but only mention the results. These are numerically calculable if we wish to know the potential in points, lying in another perpendicular cross-section than the current-electrodes. But just in the case we wish to investigate, these points

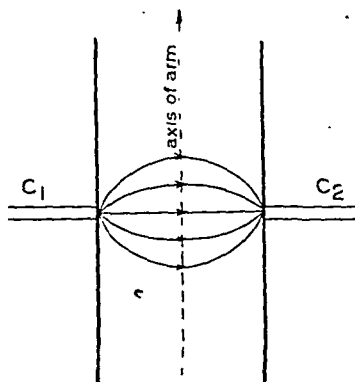


Fig. 9. Transverse current through the arm.  $C_1$  and  $C_2$  = current-electrodes.

(the measuring-electrodes) have rather to be placed in the same cross-section as the current-electrodes and then the series, which must be numerically computed, diverges. We have not succeeded in finding a solution of the mathematical problem in a form other

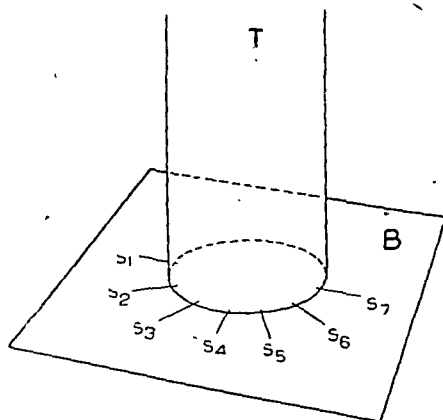


Fig. 10. Model of the arm, with seven electrodes  $S_1 \dots, S_7$ , serving for studying the transverse current.

than this diverging series. On the other hand this series represents a definite and finite function of the distance of current- and measuring-electrodes, that, once determined, can serve as a base for the interpretation of the measurements with the transverse current.

Now the same function enters into the reckoning both in the case of the anisotropic and of the isotropic medium. Therefore we could determine this function experimentally with the aid of an isotropic medium. To this purpose a cylindrical glass-tube  $T$  (fig. 10) is used, closed at its lower side with a non-conducting bottom  $B$  and filled with an electrolytical conductor of known specific resistance. A number of metal strips  $S$  between the edge of the tube and the bottom, and protruding only a little inside, serve as electrodes.  $S_1$  and  $S_7$ , situated diametrically, are the current electrodes,  $S_2 \dots S_6$  are the measuring-electrodes. Measurement of the p. d. between the latter gives values of the unknown function, mentioned above, which can be represented by a graph. This function, thus determined with an isotropic medium, may be applied for an anisotropic medium e. g. the arm.

The measurements of the resistance of the arm using a transverse current, can now be used to draw a conclusion with respect to the two specific resistances of the anisotropic medium. The mathematical analysis shows that we can compute from the experimental result with transverse current the value of the square root of both specific resistances, the longitudinal one  $\varrho_l$  and the transversal one  $\varrho_t$ . From a number of measurements with transverse current, using different distances of the measuring-electrodes, we have found:

$$\sqrt{\varrho_l \varrho_t} = 330 \Omega \text{ cm.}$$

$\varrho_l$ , the longitudinal specific resistance, can be deduced from the cases in which the current flows parallel to the axis of the arm. Formerly (p. 594) we have mentioned the value:

$$\varrho_l = 230 \Omega \text{ cm.}$$

Thus we conclude:

$$\varrho_t = \frac{330^2}{230} \Omega \text{ cm} = 470 \Omega \text{ cm.}$$

Just as we expected (p. 601) the transversal specific resistance  $\varrho_t$  is appreciably larger than the longitudinal one. The ratio  $\varrho_t/\varrho_l = 470/230 = 2.0$  is in remarkable accordance with the measurements of Sapegno (3) on frog-muscles.

The transversal specific resistance of  $470 \Omega \cdot \text{cm}$ , however, is smaller than the largest value of the apparent specific resistance

(570  $\Omega$  cm), found with the four electrodes on a straight line (p. 17) and neglecting the anisotropy. Therefore it seems probable that the two explanations, mentioned on p. 600/601 both are true. The conductivity of the muscles indeed is anisotropic and at the same time a layer of badly conducting tissue under the skin has an influence on the current-distribution.

To arrive at an exact determination of  $\rho_l$  and  $\rho_t$  it should be necessary to develop a mathematical theory of the current-distribution in an anisotropic homogeneous cylinder, enveloped by a badly conducting isotropic layer. The »resistances» measured with the four electrodes on a straight line should have been interpreted, according to this theory. The mathematical complications of this solution, however, seem to be so large, that we have not endeavored to follow this way.

## 7. Influence of outer circumstances on the specific resistance.

We have tried to influence the specific resistance of the arm and of the fingers by different outer circumstances.

a. The time during which the current passes, is varied from 4 to 15 seconds and in each case the resistance of a part of the arm is measured. The same value of the resistance is found and thus we may conclude that the interior polarization is not influenced by the time during which the current passes.

b. The fingers are heated in warm water, dried quickly and the specific resistance is measured. Then the fingers are cooled in a liquid of about  $-10^\circ$  C, dried and measured again. No appreciable difference in the two cases is found. So the filling of the fingers with more or less blood has only a slight influence on the specific resistance. This is not surprising, as the specific resistance of blood is only slightly less than that of the tissue of the fingers (see p. 606).

c. To investigate the influence of the blood-contents of the fingers in another way we have swathed a finger with an elastic bandage, measured the resistance and measured it again after releasing the pressure. In this case too the influence is too small to be stated.

d. When the resistance of a part of the arm is measured repeatedly, the values are slightly different. This may be caused by errors of the method, but it is also possible that the human body is

in somewhat different conditions on different days. Possibly the water-contents of the body is variable and thus the specific resistance of the tissues. We therefore have measured the resistance of a part of the arm alternately after a period of excessive drinking (2 liters of water in 2 hours) and of an abstinence of drinking during several hours. The difference in the resistance was not larger than the mean error in the measurement. So the small differences in the specific resistance found on different days are not to be ascribed to the differences in the amount of resorbed water, caused by more or less drinking.

*c.* Finally we have investigated whether the contraction of the muscles of the arm has any influence on its resistance. No effect whatever could be observed.

## 8. Specific resistance of the blood.

We have asked ourselves, if the blood plays an important part in the conduction of the tissues. Therefore we have measured its specific resistance with the same method as used for the human tissue. To avoid coagulation we have sometimes added 0.01 till 0.001 % of heparine. As this is no electrolyte and its concentration is very small, it has no appreciable influence on the specific resistance.

We have made each measurement with the small quantity of blood, which can be obtained by a prick with a snapper<sup>1</sup>. The blood is mixed with a small amount of a 0.1 % solution of heparine and sucked in a capillary tube with a cross-section of 1 mm<sup>2</sup> and a length of 40 mm. This is provided with four platinum electrodes of which the outer one's, nearly at the end of the tube, serve as current-electrodes, and the other two as measuring-electrodes. In this case, as formerly, polarization has no influence. The specific resistance of the blood is deduced by comparing the resistance, found in this way, with the resistance found by filling the tube with a solution of NaCl of known specific resistance. By doing so, it is not necessary to know the current-intensity, the distance of the measuring electrodes or the cross-section of the tube. The measurement

<sup>1</sup> By swinging the arm around it is possible to centrifuge so much blood to the hand that a prick of only 2—3 mm deep gives about half a cm<sup>3</sup> of blood.

is executed at roomtemperature i. e.  $18^{\circ}$ . As a mean for some different persons is found for the specific resistance of the blood to direct current at  $18^{\circ}$  a value of  $230 \Omega \text{ cm}$ . To compare this value with the one found for the tissues, it must be reduced to body-temperature of say  $37^{\circ}$ . We will accept a temperature-dependence which equals the one of NaCl, as is to be expected for the ions, prevailing in the blood. We find that the specific resistance of the blood at  $37^{\circ}$  will be 1.45 times smaller than at  $18^{\circ}$ , so blood at body-temperature has a specific resistance of  $160 \Omega \text{ cm}$ .

As is seen from this number it is not so much smaller than the mean specific resistance of our tissues. So there is no reason to suppose that the electric current in our body will follow the blood-vessels as is sometimes supposed.

It seems very curious that the specific resistance of our body, and in particular that of the blood, is so much larger than that of a physiological solution, which is equivalent with the blood in osmotic behaviour. While the specific resistance of physiological solution is equivalent with about 0.9 % NaCl, that of the blood corresponds to about 0.3 % NaCl. It is obvious that the poor permeability of the membranes of the erythrocytes to ions is responsible for this difference (4).

To investigate this influence of the erythrocytes on the specific resistance of the blood, we have centrifuged it to remove the erythrocytes. To that purpose a capillary tube was filled with blood mixed with heparine, centrifuged and broken at the boundary of the collected erythrocytes. The plasma thus separated was transported into the capillary tube with the four platinum electrodes, mentioned above and the specific resistance was measured. It appeared to be  $100 \Omega \text{ cm}$  at  $18^{\circ}$ , corresponding to  $70 \text{ cm}$  at body-temperature.

Indeed, as was to be expected, it is much smaller than the specific resistance of the blood and differs not much from that of physiological solution (about  $72 \Omega \text{ cm}$  at  $18^{\circ}$ ).

In analogy to the blood, it is without doubt the influence of the cell-membranes which makes the specific resistance of human tissue so much larger than that of physiological solution at the same temperature.

### Summary.

The specific resistance of different parts of the live human body to direct current is measured. The influence of the resistance of the skin is eliminated by measuring p. d.'s on the skin with a triode-voltmeter, which needs no current for its indication.

The values of the specific resistance of different parts of the body diverge not strongly and are larger than is to be expected for a physiological salt-solution. This must be ascribed to the influence of the cell-membranes.

The bones in the arm cannot account for the differences of specific resistance along the arm. The elbow-joint has no extra-resistance.

The skull has an appreciable isolating influence. The current, however, can rather easily enter into the brains through the temples.

Anomalies of the conductance of the arm can be explained by an isolating layer of fat around the arm and by an anisotropy of the electric conductance through a muscle.

The trunk is less conducting than the arm. For a part this has to be attributed to the air in the lungs.

The blood is only slightly better conducting than the mean human tissue. So a current will not go preferably along the blood-vessels.

The blood-plasma conducts better than the blood, as the membranes of the erythrocytes, which are not easily penetrated by ions, are absent.

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